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HIGH LEUCOCYTOSIS (LEUKAEMOID REACTIONS ?) IN DERMATITIS HERPETIFORMIS.

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RELATIVE eosinophilia is common in dermatitis herpetiformis but absolute leucocytosis is not considered a characteristic feature. On those occasions when it has been noted, examination of the blood has not often been repeated. Engman and Davis (1915) detailed 35 blood counts in 27 patients suffering from this disease : in 3 out of 14 patients in whom total white cell counts were performed there was a leucocytosis of from 14,000 to 32,000 cells per cu. mm. Riecke (1931) tabulated the results of 80 blood counts in 47 patients. There was a leucocytosis in 13 out of 43 patients, the highest count being 30,200 cells per cu. mm. In both series the most common abnormality of the differential count was eosinophilia, although sometimes an increased percentage of monocytes or a moderate increase of lymphocytes was recorded.

In each of the three cases of dermatitis herpetiformis we describe here, high leucocytosis was a striking feature, with peaks of from 37,000 to 68,000 cells per cu. mm. No acute infective or other process was present to explain this rise. The differential counts were also abnormal, leading in one case to a strong suspicion of the presence of lymphatic leukaemia. The blood was examined at very frequent intervals during the patients' stay in hospital and examinations were performed after their discharge.

CASE REPORTS.

Case 1.—A woman aged 42 years was admitted with a widespread, itching, bullous eruption of one year's duration. The family and previous history were not relevant apart from the fact that from childhood she had a " tendency to be anaemic ". On examination, there were numerous vesicles and bullae up to 2 cm. in diameter, with

serous contents, widely and symmetrically distributed over the face, trunk and limbs. They showed a tendency to herpetiform grouping. A few erosions and urticarial lesions were seen. There were no oral lesions. The Nikolsky test was negative.

The supraclavicular, axillary, inguinal and femoral lymph glands were enlarged and slightly tender. The firm edge of the spleen was palpable three fingers' breadths below the left costal margin. The liver was not enlarged. The blood pressure was 100/60 mm. Hg and the sedimentation rate 8 mm. in 1 hour (Westergren). The urine and stool were normal. The blood concentrations of urea, uric acid, glucose, free and total cholesterol and proteins were in the normal range, as were the results of a number of liver function tests. Serological tests for syphilis were negative. There was no essential change when these examinations were repeated during her stay in hospital. Patch tests with 50% potassium iodide were sometimes positive and sometimes negative. Serum from a bulla contained many eosinophils and was sterile on culture. Biopsy specimens from lesions on the forearm and back revealed tense subepidermal blisters, one containing numerous eosinophils, a picture consistent with a diagnosis of dermatitis herpetiformis.

Because of continuing abnormality, blood counts were repeated about every four days, 27 examinations being made during 107 days (Fig. 1). On the day of admission there were 5,500,000 erythrocytes per cu. mm., with a haemoglobin of 13 g. %. Bleeding and clotting times were normal. Leucocytes numbered 22,100 per cu. mm., with 35% neutrophils, 54% lymphocytes, 2% monocytes and 9% eosinophils. In all subsequent examinations there were no abnormalities in the red-cell series, but the leucocytosis persisted and fluctuated in an unstable manner, sometimes varying by

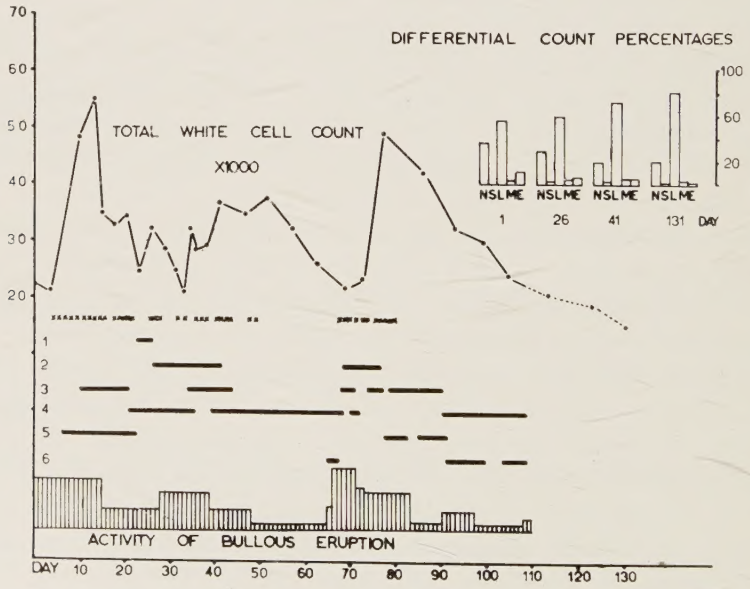
DIFFERENTIAL COUNT PERCENTAGES
TOTAL WHITE CELL COUNT
X1000
NSLME NSLME NSLME NSLME
1 26 41 131 DAY
ACTIVITY OF BULLOUS ERUPTION
DAY 10 20 30 40 50 60 70 80 90 100 110 120 130

FIG. 1.—*Case* 1.—Broken line represents blood counts performed after discharge, × × × febrile episodes.

1. sulphadiazine, 0·75–3·0 g. daily.
2. sulphapyridine, 0·05–2·0 g. daily.
3. A.C.T.H., 30–150 units daily.
4. cortisone, 50–400 mg. daily.
5. antibiotics, proc. penicillin, aureomycin, terramycin.
6. carbarsone, 0·25–0·5 mg. daily.

N = neutrophils.
L = lymphocytes.
E = eosinophils.
S = band forms.
M = monocytes.

10,000–20,000 cells per cu. mm. within a day or two. The highest white cell count recorded was 54,000 per cu. mm. There was a marked lymphocytosis often exceeding 70%. Sometimes many young lymphocytes were present and on two occasions lymphoblasts were also seen. The initial mild eosinophilia did not persist.

Bone marrow examination one week after admission showed a large number of mature lymphocytes, a small percentage of which were atypical. There were also large numbers of eosinophils. A second examination one week later, when the blood leucocytosis had reached 54,000 per cu. mm., showed numerous mature and immature lymphocytes and gave the impression of lymphatic leukaemia.

The patient was treated with penicillin, sulphadiazine, sulphapyridine, aureomycin, terramycin, A.C.T.H., cortisone, vitamins and carbarsone, as indicated in Fig. 1. Her skin condition fluctuated in severity, there being at times almost no active lesions and at others an extensive, severely itching, bullous eruption. Healed lesions usually left markedly pigmented areas. She had bouts of pyrexia, not always associated with exacerbation of her skin condition and tended to suffer from insomnia, headaches, nausea and abdominal discomfort, hypotension and vertigo. She also developed angular stomatitis. Her weight increased from 57 kg. (125½ lb.) to 61·5 kg. (135 lb.), and there was marked " mooning " of the face resulting from the steroid therapy. No septic foci were found except in the teeth, one of which, extracted because of a root granuloma, yielded *Staphylococcus aureus* and a non-haemolytic streptococcus on culture.

The lymph glands and spleen gradually decreased in size and after 2 months were no longer enlarged. When the patient was discharged her skin condition had greatly improved and the leucocyte count was falling steadily, but there was little change in the differential picture. She continued to receive steroid and sometimes other treatment, the doses being gradually reduced to 5–10 mg. prednisone daily and 20 units A.C.T.H. gel intramuscularly twice weekly. She has since remained under close medical supervision. The leucocyte count fell to normal levels about 9 months after discharge, but a high lymphocytosis persisted for about 4½ years. However, for more than the past two years the blood count has been normal in every respect except for signs of a mild hypochromic macrocytic anaemia.

The patient was readmitted to hospital for a few days almost seven years after her original admission. Her general health was good and she weighed 54·5 kg. There were a few small erythematous patches up to 4 cm. in diameter on the chest and back and there were similar areas with closely set vesicles on the inner side of the right thigh. Since discharge from hospital she had periodically suffered from such eruptions, which were always accompanied by itching. The inguinal and one of the axillary lymph glands were slightly enlarged. The liver edge was palpable 2 cm. below the right costal margin and the spleen edge could be felt on deep inspiration. Blood pressure was 100/70 mm. Hg and the sedimentation rate 5 mm. in the first hour (Westergren). Blood chemistry values and liver function tests were normal. The blood picture showed 3,960,000 erythrocytes per cu. mm. with 11·4 g. % Hb. Serum iron was somewhat low, 54 γ %. Leucocytes numbered 7,200 per cu. mm. with 73% neutrophils, 22% lymphocytes, 3% monocytes and 2% eosinophils. Bone marrow examination revealed normal erythrocyte, leucocyte and megakaryocyte series. There was a slight increase of reticulum and plasma cells. The haematologist, who examined the patient as well as studying her blood and bone marrow, concluded that there was now no evidence of any malignant haematological disorder.

Case 2.—A man aged 73 years was admitted with a widespread, itching, bullous eruption of 6 months' duration. There was nothing of relevance in the family history. The patient had been operated upon for haemorrhoids 45 years previously, for a thyroid condition sixteen years ago and for removal of stones from the urinary bladder on three occasions between fourteen and eight years prior to admission. Gastrectomy

had been performed nine years and prostatectomy three years previously. The patient's general state on admission was rather poor and although 175 cm. tall he weighted only 59 kg. There were many vesicular and bullous lesions on the face and lower limbs, whilst the skin of the rest of the body was erythematous with numerous erosions and serous or bloody crusts. No oral lesions were present. The Nikolsky test was negative. Physical examination revealed little of note. The blood pressure was 120/80 mm. Hg and the sedimentation rate 10 mm. in the first hour (Westergren). Urine and stool examinations were normal. The blood total serum protein was 5·5 g. %, with albumin 2·5 g. % and globulin 3·0 g. %. The blood cholesterol was also low, 125 mg. %. Blood urea was 40 mg. %. Serum alkaline phosphatase varied from 5·9 to 7·1 Bodansky units. Serological tests for syphilis were negative. L.E. cells were not detected in the peripheral blood. Radiography of the chest was normal. The electro-cardiogram indicated an incomplete right bundle branch block ; there was no evidence of cardiac infarction. Patch tests with 50% potassium iodide were negative. Histological examination of vesicular lesions from the back and buttock showed tense subepidermal blisters, consistent with a diagnosis of dermatitis herpetiformis.

Blood counts were repeated approximately every 4 days for the first two months, a total of 21 examinations being made. On the day of admission there was hypochromic anaemia, the red cells numbering 3,070,000 per cu. mm., with a haemoglobin of 9 g. % and a leucocytosis of 15,000 per cu. mm., comprising 56% neutrophils, 37% lymphocytes, 2% monocytes and 5% eosinophils. The hypochromic anaemia persisted for the first few weeks, with poikilocytosis and marked anisocytosis. The white cell count rose steeply during the first month to reach a peak of 37,000 per cu. mm. (Fig. 2). This was the period of most active eruption of new lesions. From this

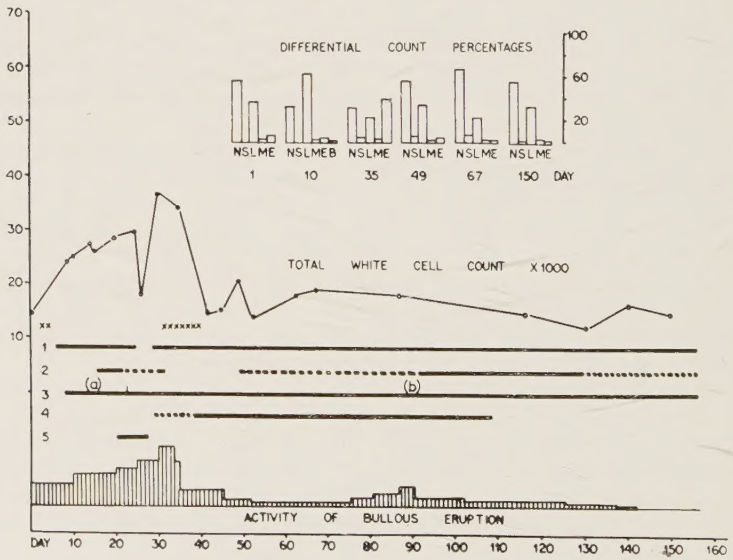

FIG. 2.—*Case* 2.—Febrile episode, × × ×.

1. sulfapyridine, 1·5–4·0 g. daily.
2. A.C.T.H., 10–30 units daily or (broken line) 2–3 times weekly.
3. (a) cortisone, 100–250 mg. daily.
   (b) prednisone, 15–50 mg. daily.
4. antibiotics, terramycin, synthomycetin, proc. penicillin, streptomycin (broken line = twice weekly).
5. diaminodiphenyl-sulphone, 50–100 mg. daily.

N = neutrophils.
L = lymphocytes.
E = eosinophils.
S = band forms.
M = monocytes.
B = basophils.

point, coinciding with much reduced activity of the skin condition, the leucocyte count fell, although it remained above 12,000 per cu. mm. The differential count was unstable, lymphocytes varying from 22%–61% and the eosinophils, although usually below 12% rose to 40% on one occasion. When the total leucocyte count fell to below 20,000 per cu. mm., the differential count became stabilised in a normal pattern. No pathological white cells were detected. Bone marrow smears revealed no pathological features.

The patient received a protein rich diet, and sulphapyridine and prednisone daily. A.C.T.H. gel was given intramuscularly twice weekly. For a week he received diaminodiphenyl-sulphone (dapsone). Supportive therapy consisted of vitamins, potassium chloride, oestrogens, androgens and broad-spectrum antibiotics. Whilst in hospital, various mishaps befell this elderly patient. On the 30th day he fell and fractured the neck of his right femur, posing special problems due to his age and to the fact that new bullous lesions were still appearing on the thighs and buttocks. His general condition worsened and he developed large pressure sores. Extension was abandoned, two blood transfusions were given, and as soon as possible he was nursed in a wheel chair. His health then improved and new skin lesions ceased to appear. Shortly afterwards his voice became weak and hoarse, he complained of difficulty in swallowing and food and drink regurgitated into his nose. Neurological examination revealed paresis of the muscles supplied by cranial nerves IX, X and XI with marked tetraparesis, probably due to polyneuritis. On laryngoscopy the right vocal cord was seen to be swollen. A biopsy specimen from this swelling revealed amyloid material. Tracheotomy was performed on the 91st day after admission and the patient fed by a stomach tube. After about six weeks his condition improved and the tracheotomy tube was removed. When the patient was discharged to a convalescent home he was free of skin lesions. He continued to receive 2 g. of sulphapyridine and 15 mg. of prednisone daily.

Thirteen months after discharge the patient's general state was very good. He felt in almost normal health and had few skin lesions. He could swallow without difficulty and was able to walk slowly with the aid of sticks. The blood count was normal except for signs of hypochromic anaemia and a slight lymphocytosis, the figures being erythrocytes 4,170,000 per cu. mm., haemoglobin 9·3 g. %, leucocytes 8,150 per cu. mm. with 51% neutrophils, 45% lymphocytes, 2% monocytes and 2% eosinophils.

Case 3.—A woman aged 62 years was admitted with a widespread, severely itching, bullous eruption of two weeks' duration. There was nothing of relevance in the family history. She tended to suffer from bronchopneumonia in the winter and shortly before admission had been treated for this condition with a number of broad-spectrum antibiotics and streptomycin. Two months previously she had also suffered from abdominal pains and haematuria. On examination a large number of vesicles and bullae, up to 2 cm. in diameter, were seen to be widely dispersed over the neck, trunk and limbs. Eroded exudative patches were present in some areas and over the shins there were a number of verrucous plaques. There were no lesions in the mouth. The Nikolsky test was negative. General physical examination revealed chronic sinusitis, but otherwise nothing of note. The patient's temperature was normal, her blood pressure 135/90 mm. Hg and the sedimentation rate 10 mm. in the first hour (Westergren). Repeated urine tests frequently showed traces of albumin, occasionally of glucose and sometimes leucocytes and granular and epithelial casts. *E. coli* and weak growths of *B. proteus* and of staphylococci were demonstrated on culture of catheter specimens. Cultures for *M. tuberculosis* were negative. Creatinine clearance was 73 ml./min. The stool examination was normal. The blood concentrations of urea, uric acid, glucose, total protein and albumin and globulin, total cholesterol and electrolytes were within the normal range. The glucose tolerance curve was normal. The results of liver function tests were cephalin flocculation, one plus ; thymol

flocculation, one plus ; thymol turbidity, 6·2–9·0 units ; Weltman, 9·0 ; bilirubin, 0·7 mg. % ; alkaline phosphatase, 8 Bodansky units. Electrophoresis of the serum proteins showed a moderate gammaglobulinaemia of 26·7%. X-ray examination of the urinary passages without contrast material revealed three small calcified shadows. Intravenous pyelography was not performed because of a reluctance to inject iodine containing compounds into a patient suffering from dermatitis herpetiformis. A radiograph of the chest showed calcification of the aortic knob and a slight emphysema. The electrocardiogram was normal. Biopsy specimens from lesions on the back showed tense subepidermal blisters, consistent with a diagnosis of dermatitis herpetiformis.

Blood counts were performed 16 times during her hospital stay of 88 days. Erythrocytes numbered 3,488,000–4,870,000 per cu. mm. with haemoglobin 10·9 g. %–13·4 g. %. Bleeding and clotting times were normal. Shortly after admission there was a leucocytosis of 23,400 per cu. mm. On the 15th day there were 19,000 white cells per cu. mm., comprising 56% neutrophils, 10% lymphocytes, 1% monocytes and 33% eosinophils. The count then rose steeply to a total of 68,000 white cells per cu. mm. by the 23rd day. By the 40th day it had fallen to normal limits and after a further moderate rise was falling again at the time of discharge. The differential count was abnormal throughout, the neutrophil and eosinophil levels tending to vary in inverse proportion (Fig. 3). On some occasions, metamyelocytes and myelocytes were seen. Both the early steep and the second more moderate rise in the total counts were associated with severe exacerbations of the skin condition. Bone marrow smears contained numerous mature and immature eosinophils, but were otherwise normal.

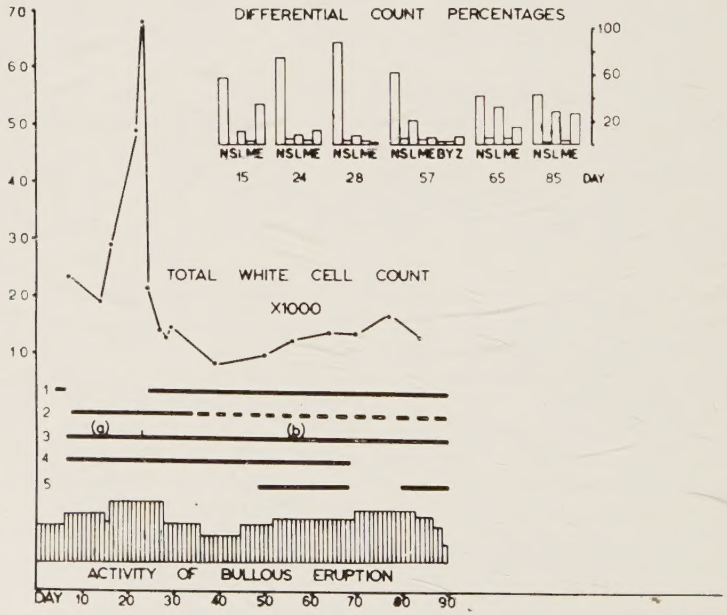

FIG. 3.—*Case* 3.

1. sulphapyridine, 1·0–3·0 g. daily.
2. A.C.T.H., 10–50 units daily or (broken line) twice weekly.
3. (a) cortisone, 200 mg. daily.
   (b) prednisone, 5–50 mg. daily.
4. antibiotics, synthomycetin, erythromycin, albamycin, streptomycin.
5. diaminodiphenyl sulphone, 50–100 mg. daily.

N = neutrophils.
L = lymphocytes.
E = eosinophils.
S = band forms.
M = monocytes.
B = basophils.
Y = metamyelocytes
Z = myelocytes.

Sulphapyridine was first administered, but was suspended after two days since many more bullae continued to appear. Oral cortisone and intramuscular A.C.T.H. gel were then given daily, together with antibiotic and other supportive therapy. There was no improvement in the patient's skin condition and sulphapyridine treatment was resumed on the 25th day. The lesions now began to clear, although the itching remained intense. About a fortnight later there was a severe relapse, and diamino-diphenyl-sulphone was given in addition to the other drugs. Cortisone had meanwhile been replaced by prednisone, the dose of which was fairly rapidly reduced from 50 mg. to 10 mg. daily. Local treatment was chiefly with a paste containing an asphaltite from the Dead Sea ("Bitupal"). She began to suffer from nervousness, excitement and tachycardia. The liver became enlarged and sensitive and râles were present over the lung bases. The signs suggested mild congestive heart failure. A further electrocardiogram revealed no evidence of cardiac infarction. On about the 80th day a marked and this time much more rapid improvement occurred. All the skin lesions dried up and healed, although the itching persisted. After discharge the patient continued to receive 7·5 mg. prednisone, 2·0 g. sulphapyridine a 100 mg. diamino-diphenyl-sulphone daily.

When re-examined one year later her general condition was good. She still suffered from fairly frequent but minor eruptions of grouped vesicles or bullae on the lower trunk or limbs, accompanied by itching. The blood picture had meanwhile returned to normal, the values being erythrocytes 4,420,000 per cu. mm., with haemoglobin 11·8 g. %; leucocytes 9,100 per cu. mm. with 50% neutrophils, 8% band forms, 36% lymphocytes, 4% monocytes and 2% eosinophils.

Discussion.

In each of these three cases there seemed to be a relationship between the high leucocyte counts and the state of the cutaneous disease. The sudden rises in the white cell count in the first patient tended to coincide with periods of renewed activity and spread of the bullous eruption. Although they were often associated with febrile episodes there was no obvious infective process to explain these events. A secondary infection would also have been expected to stimulate a neutrophil rather than a lymphocyte response. The high lymphocytosis of nearly 80% was present in spite of almost continuous and intensive treatment with A.C.T.H. or cortisone, which generally lower the lymphocyte count. This picture, with the associated enlargement of the superficial lymph glands and spleen and the bone marrow abnormalities, strongly suggested lymphatic leukaemia. However, although immature lymphocytes were seen, truly pathological cells had never been detected in the peripheral blood or the bone-marrow. Nor was there any marked disturbance of the erythrocyte count or haemoglobin. The subsequent clinical history of the patient, together with the gradual return to normal of the total and differential leucocyte counts and of the bone-marrow picture, are also against this diagnosis. If this blood picture cannot be satisfactorily explained as either a simple leucocytosis or as a true leukaemia, it seems justifiable to place it amongst the leukaemoid reactions, first described under this name by Krumbhaar (1926).

In the case of the second patient, the leucocytosis was less marked, but once again the highest counts and periods of greatest instability in the count were associated with periods of activity of the bullous skin eruption (Fig. 2). Although this patient's blood picture might more justifiably be called merely a high leucocytosis, the marked instability of both the total and the differential counts are unusual features. Nor was there any evidence of secondary infection responsible for the neutrophil response. It too might be possibly considered a leukaemoid reaction.

The third patient developed the highest leucocyte count of all, rising to 68,000 cells per cu. mm. This " peak " and the later more moderate rise were associated with worsening of the bullous skin eruption. The differential count remained markedly unstable. Although at the height of the leucocytosis the predominant white cell was the neutrophil, apart from the persistent *E. coli* and staphylococcal urinary infection which had preceded the skin eruption, there was no obvious acute infection and at no time were there febrile episodes. The height of the leucocyte count, the appearance of immature forms in the peripheral blood and the subsequent return to normal make it acceptable to classify this reaction as " leukaemoid ".

Hill and Duncan (1941) arbitrarily define a leukaemoid reaction as one in which the total leucocyte count exceeds 50,000 per cu. mm., or in which immature cells of the " blast " stage are present. Hilts and Shaw (1953) consider a count of over 50,000 white cells per cu. mm., either alone or combined with more than 2% myeloblasts or myelocytes, as a myeloid type of leukaemoid reaction. They accept a lymphocytosis of over 40% with the presence of immature forms as indicative of a lymphoid leukaemoid reaction. The latter authors found only 49 well documented cases in the English literature, but note that the condition probably occurs more often than the number of published accounts would suggest. Recently, new techniques which may assist in differentiating certain forms of leukaemoid reactions from true leukaemic states have been described. These include studies of the blood histamine level (Valentine, Pearce and Lawrence, 1950) ; blood vitamin B_{12} level (Mollin and Ross, 1955 ; Beard, Pitney, Sanneman, Sakol and Moorhead, 1954 ; Beard, Pitney and Sanneman, 1954 ; Rachmilewitz, Izak, Hochman, Aronovitch and Grossowicz, 1957), and an evaluation of leucocyte alkaline phosphatase activity (Kaplow, 1955 ; Leonard, Israëls and Wilkinson, 1958).

Hill and Duncan (1941) classified leuk moid reactions into three main groups according to the apparent causative mechanism :

i. Bone marrow irritation or stimulation, physical, chemical or allergic.
ii. Liberation leucocytosis, being a bone marrow response to overwhelming demand.
iii. Ectopic haematopoiesis, usually due to destruction or crowding of the bone marrow.

Diseases and other conditions reported as occasionally stimulating leukaemoid reactions include tuberculosis, bacterial, viral and protozoal infections, certain anaemias, non-myelogenous malignant tumours and local or systemic administration of potentially toxic drugs. It has rarely been associated with a primarily dermatological disease and to our knowledge has never been described together with dermatitis herpetiformis. The etiology of dermatitis herpetiformis being entirely unknown it is difficult to postulate by which of the above mechanisms the disease might be held responsible for leukaemoid reactions. Direct responsibility, if such exists, is most probably limited to predisposed individuals. It is also possible that dermatitis herpetiformis may at times be an expression of some underlying primary haemopoietic disturbance, or perhaps of some other disturbance which may secondarily affect the haemopoietic system.

The possible rôle of drugs must also be considered. The three patients all received treatment with sulphapyridine, A.C.T.H., cortisone or prednisone and various antibiotics. Two were also given diamino-diphenyl-sulphone and one carbarsone. A study of Figs. 1–3, together with an evaluation of the effects of these various drugs on other patients, renders sulphapyridine especially suspect. Leukaemoid reactions due to sulphapyridine or sulphanilamide were reported during the period when these drugs were widely used (Moody and Knouf, 1939 ; Goldbloom, Greenwald and Reinstein, 1941).

Although there is now some tendency to re-introduce sulphonamide preparations because of the development of bacterial resistance to wide spectrum antibiotics, sulphapyridine itself is rarely employed except for dermatitis herpetiformis. In each of the patients described some relationship can be made out between the leucocyte response and sulphapyridine administration. In the case of the first patient the initial leucocytic " peak " might possibly be related to known administration of this drug before admission. She was reported to have reacted to its use by the development of fever, rigors and lowered blood pressure. With the second patient the leucocyte response subsided even though sulphapyridine administration was continued. This, however, might have been due to some adaptive mechanism. The third patient was initially given the drug for two days only, about a week and a half before the sharp rise in the leucocyte count. When re-adminstered the count did not rise again, although instability was still evident in the differential picture and in the appearance of immature white cells in the peripheral blood. If these reactions are indeed due to sulphapyridine, it is uncertain whether they should be explained on a toxic, stimulative or allergic basis.

Summary.

Three cases of severe bullous dermatitis herpetiformis are reported in which frequently repeated blood counts revealed high leucocytosis of from 37,000 to 68,000 cells per cu. mm.

The differential blood counts were pathological and one case resembled lymphatic leukaemia.

It is suggested that these be regarded as leukaemoid reactions.

The possible causative rôle of the disease processs or of the drugs used in its treatment is briefly discussed.

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SÉZARY'S SYNDROME.

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Erythroderma has many causes, among which proliferative disorders of the reticuloendothelial system form an important group. In this group, seven cases of an apparently distinct syndrome have recently been described (Sézary and Bouvrain, 1938 ; Sézary, Horowitz and Maschas, 1938 ; Baccaredda 1939 ; Sézary and Bolgert, 1942 ; Sézary, 1949 ; Wilson and Fielding, 1953 ; Alderson, Barrow and Turner, 1955). This condition is characterised by generalized erythroderma and the presence of large monocytoid cells in the skin and blood and has been referred to as Sézary's syndrome.

The purpose of this paper is to report two further cases and to discuss the criteria for diagnosis and the haematological features of the condition.

Case Reports.

Case 1.—A housewife aged 56 years.

The presenting symptom, noticed in August 1952, was thickening and fissuring of the plantar skin associated with slowly increasing deformity of the toenails which were yellow, opaque, curved downwards, thickened, rough and brittle. Some weeks later, itchy, tender, red, scaly patches appeared on the legs and thighs. In January 1953 the trunk, arms and scalp were similarly affected. The palms then became thickened and fissured, and the fingernails showed changes similar to those of the toes. By June 1953, there was generalized erythroderma, loss of weight and increasing tiredness. There was no excessive sweating.

She had had jaundice, probably infective, in 1938 but there had been no recent illness or mental upset. She had never had skin trouble before and her family history was negative.

On admission to hospital (8.vi.53), the skin showed generalized erythroderma with branny exfoliation and scattered, circular, indurated, tender plaques, up to two inches in diameter. There was marked hyperkeratosis and fissuring of the palms and soles. All the nails were sharply convex, greatly thickened, yellowish in colour, opaque, rough and brittle. No mycelium was found in scrapings of the skin and nails. There was no pubic or axillary hair ; on scalp and eyebrows it was very sparse. There was slight bilateral ectropion. A mask-like appearance of the face was produced by the thickening of the supra- and infra-orbital skin (Fig. 1). The cervical, axillary and inguinal lymph nodes were slightly enlarged, firm and discrete, but neither

FIG. 1.

painful nor tender. The liver edge was palpable one finger's breadth below the right costal margin but there was no evidence of splenic enlargement. Apart from moderate hypertension (175/108) there were no other abnormal physical signs. A skiagram of the chest did not show any enlargement of the mediastinal glands.

Laboratory data (see Table I).

Blood films.—Leucocytes: of these 82% (37,720) were thought to be atypical large lymphocytes. Eosinophils 1% (460). Erythrocytes normal, platelets numerous.

Marrow biopsy (sternal).—Smears and sections showed similar atypical cells, but these were no more numerous than could be accounted for by the presence of peripheral blood.

Skin biopsy.—Sections showed a dense infiltration of the upper and middle layers of the corium by "mononuclear cells".

A diagnosis of atypical chronic lymphatic leukaemia was made and it was suggested in view of the marrow findings that the skin might be the site of origin of the neoplasia. Wide field radiotherapy to a total of 1753 r was given over four weeks. Her skin improved with great decrease in itching. The scaling of her body subsided but the skin of palms and soles remained thickened and the nail changes persisted. The total leucocyte count fell from 46,000 per cu.mm. to 34,000 per cu.mm., the reduction being mainly in the atypical cells. The haemoglobin rose from 12·5 g.% to 13·6 g.%. A similar but shorter course of radiotherapy was given from 23.xi.53 to 16.xii.53

as her condition had deteriorated. Again there was improvement and the leucocyte count fell from 56,000 to 13,500 per cu.mm.

The skin caused little discomfort until October 1955 when further radiotherapy was required for the hands, feet and neck. At this time a reassessment of the blood findings led to the diagnosis of Sézary's syndrome. From April 1956 the skin again became red and itchy with pronounced scaling. Prednisolone 5 mg. b.d. was given: this almost completely controlled the itching and the erythema subsided. This dose was adequate for some time but on 27.iii.57 she had to be readmitted and the dose of prednisolone was increased to 25 mg. daily before adequate improvement occurred.

She was discharged from hospital, but the condition of her skin slowly deteriorated, even with the increased dose of prednisolone. Since the beginning of her illness, her general health had not been particularly severely affected. However, in November 1957 she began to complain of tiredness, swelling of the abdomen and legs and loss of weight. She was readmitted on 20.xii.57, obviously ill and emaciated with generalized erythema and scaling, most marked over the lower half of her trunk. The lower limbs and sacral area were oedematous. The abdomen contained free fluid. An irregular liver edge was palpable fully three fingers' breadths below the costal margin and the spleen was just palpable. Over the umbilicus there was a firm painless nodule about 1 cm. in diameter. The nodule was excised and shown by histological examination to be a well differentiated adenocarcinoma whose likeliest primary source was the colon. A peritoneal tap showed much blood with carcinomatous cells, leucocytes, serosal cells and a small number of atypical monocytoid cells (almost certainly Sézary cells.) The patient died cachectic on 13.i.58.

Post mortem examination showed an ulcerating tumour in the descending colon apparently arising in, but not obstructing, the bowel. Metastases were present in the left colic lymph nodes, the mesenteric lymph nodes, the liver, the ovaries and on the peritoneal surfaces of omentum, mesentery, diaphragm, lateral and anterior abdominal walls. Massive haemorrhagic ascites had raised the diaphragm causing causing partial collapse of both lungs. Neither naked-eye nor microscopical examination of imprints of marrow (sternal, costal, vertebral and femoral), spleen and lymph nodes (cervical, thoracic, abdominal, axillary and inguinal) showed any evidence of a leukaemic infiltrate. Histological examination showed glandular carcinoma of colonic origin. As far as we are aware the occurrence of this neoplasm is coincidental.

Case 2.—A retired labourer aged 78 years.

The patient had led an active life until 1951, when he developed generalized pruritus and had difficulty in walking because of thickening of the soles of the feet. He was then found to have diabetes mellitus. Treatment with insulin and diet led to lessening of the itching, but chronic eczematous patches developed on his hands, arms and legs in 1953. Local treatment improved the skin lesions.

In March 1956 he was admitted to hospital as a case of generalized erythroderma, with loss of weight (four stones in three years). His skin was red with fine branny desquamation. The soles and palms were thickened. The axillae, chest and pubic regions were hairless and his head was sparsely covered. Bilateral, moderate ectropion was present. The cervical, axillary and inguinal lymph nodes were discretely enlarged but not tender. The fingernails and to a lesser extent the toenails were yellow, convex, thickened, rough and brittle. No mycelium was found in scrapings of the skin and nails. Sporadic " sweating " occurred in the small of his back but the rest of the skin was dry. The " sweat " was sticky, but the affected region had the same appearance as other parts. The liver edge was felt three finger's breadths below the right costal margin. The spleen was not palpable. The blood pressure was 200/110. Radiography showed no enlargement of the heart or mediastinal lymph nodes. The blood picture was within normal limits (Hb., W.B.C. and ordinary Leishman stained film). For

other laboratory findings see Table I. No histological examination of the skin was made at this time.

His diabetes was stabilized with diet and insulin. With control of the diabetes, the erythema and itch became less and on 6.vi.56 he was discharged from hospital. He remained comfortable for some months after, but although his diabetes was controlled, his skin continued to exfoliate. Itching became intolerable. The thickened skin on his soles cracked and he was unable to walk. His elderly wife could not nurse him and on 28.viii.57 he was readmitted, when the clinical picture was similar to that at his first admission.

Laboratory data (See Table I).

Blood films.—Leucocytes: 5% were of large monocytoid type similar to those in Case 1. Some were binucleate. Erythrocytes normal, platelets numerous.

"*Buffy coat*" *films* (*from haematocrit*).—The Sézary cells, as well as the other leucocytes, were concentrated in these preparations and thus were more conveniently studied.

TABLE I.—*Laboratory Findings.*

	Case 1.			Case 2.		
	8.vi.53	27.iii.57	20.xii.57	27.iii.56	28.viii.57	21.iii.58
Urine:						
Protein	neg.	neg.	neg.	neg.	neg.	neg.
Sugar	neg.	neg.	neg.	+	+	trace on one occasion
Blood:						
Urea (mg./100 ml.)	37·0	26·0	26·0	41·0	—	30·0
Sugar (mg./100 ml.)	—	—	96·0	maximum 227	maximum 311	fasting 160
Total plasma proteins (g./100 ml.)	—	7·1	6·4	7·7	7·3	6·3
Albumin (g./100 ml.)	—	3·2	2·1	4·0	3·9	3·0
Globulin and fibrinogen (g./100 ml.)	—	3·9	4·3	3·7	3·4	3·3
Alkaline phos. (K.A. units)	—	10·5	44·5	20·0	21·5	7·0
Acid. phos. (K.A. units)	—	—	—	2·0	—	3·9
Cephalin flocculation	—	+	++	neg.	+++	neg.
Thymol turbidity (units)	—	2·0	1·0	1·0	2·0	2·0
Plasma bilirubin (mg./100 ml.)	—	0·4	0·7	0·3	0·4	0·25
Wassermann reaction	neg.			neg.		

Skin Sections.—In the upper third of the dermis, there was a dense infiltrate of large mononuclear cells, with scattered polymorphs and lymphocytes. There was parakeratosis and acanthosis of the epidermis with a few small foci of mononuclears (Fig. 2).

Even with insulin, itching persisted and prednisolone 5 mg. t.i.d. was given, despite its potential diabetogenic activity. The erythroderma and itching lessened. The patient was discharged on 30.x.57, but his condition worsened at home where conditions were unsatisfactory. He was readmitted on 21.iii.58, when, again, he was helped by prednisolone, but to a lesser degree than previously. In order to allay the persistent itching, wide field radiotherapy to a total of 290 r was given to the trunk over six weeks. There was considerable improvement which is maintained. At present his general health is not impaired; in particular he is not anaemic, unlike the majority of cases of chronic leukaemia complicated by skin lesions. Prednisolone

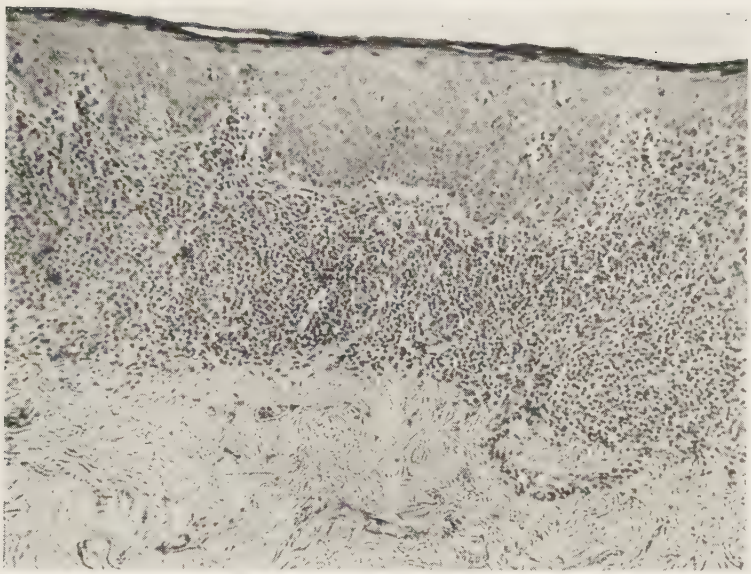

Fig. 2.

is no longer being given and the urine is usually sugar free on restricted carbohydrate diet alone. The last blood examination on 3.xii.58 showed Hb. 98% (14·6 g.); P.C.V. 45%; M.C.H.C. 32%; W.B.C. 7,000 per cu.mm.; differential leucocyte count: Sézary cells 1·5%; eosinophils 5·0%.

Discussion.

Only nine cases of Sézary's syndrome (including our two) have so far been described. The main clinical features are intense pruritus, generalized erythroderma and superficial lymphadenopathy. According to the original description (Sézary and Bouvrain, 1938) and to the paper of Alderson *et al.* (1955) the diagnosis is made by demonstrating a dense mononuclear infiltrate in the dermis and the presence in the blood of unusually large monocytoid cells (the so-called Sézary cells). The clinical features are not yet sufficiently well defined to allow the establishment of Sézary's syndrome as a specific entity and the histological appearances of the dermal infiltrate are not quite characteristic enough for a precise diagnosis. Thus, until more cases have been thoroughly studied throughout their whole course and more is known about the histopathology, the diagnosis must rest entirely on the cytology. It is therefore essential that the specificity of the Sézary cell be established.

The Sézary Cell.—In thin air-dried films, the characteristic cells range from about one to one and a half times the size of a normal circulating monocyte, but because of variation in the degree of flattening during spreading of the films, any dogmatic statement on their size is scarcely justifiable, at least as

judged by simple methods. The nucleus is large (about twice the size of a lymphocytic nucleus) and in Leishman stained preparations it is an intense dark blue, with a chromatin arrangement rather like that of a small lymphocyte, but here the likeness ends. The nucleus may be round, ovoid or reniform with indentations or convolutions. Binucleate and very rarely trinucleate forms are seen. With Romanowsky stained preparations, nucleoli are only rarely seen. Peculiarly coarse aggregations of chromatin, twisting and interlocking in a pattern reminiscent of the cerebral convolutions, are always present in some of the cells (Fig. 3). The cytoplasm is usually remarkably

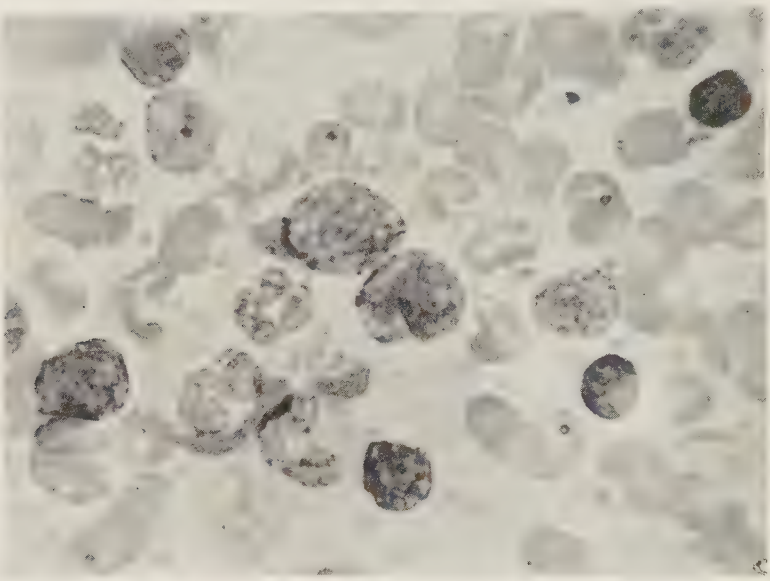

FIG. 3.

pale and clear though occasionally there may be slight basophilia. We have seen, as was noted in other cases, that a few cells show a fine dusting of granules, but we feel that these cells should not be classified as typical. From our limited experience we have come to the interim conclusion that the most characteristic of the variants of the Sézary cell is that with a densely staining cerebriform nucleus and pale, clear cytoplasm—so pale and so clear that it is more translucent than the plasma surrounding it (Fig. 4). The characteristic cells are peroxidase negative. We also found using systems containing opsonised erythrocytes that these cells did not appear to have phagocytic properties. This correlation is not unexpected. The nuclei of the typical cells give a positive Feulgen reaction for desoxyribonucleic acid: the less condensed nuclei give a weaker positive reaction.

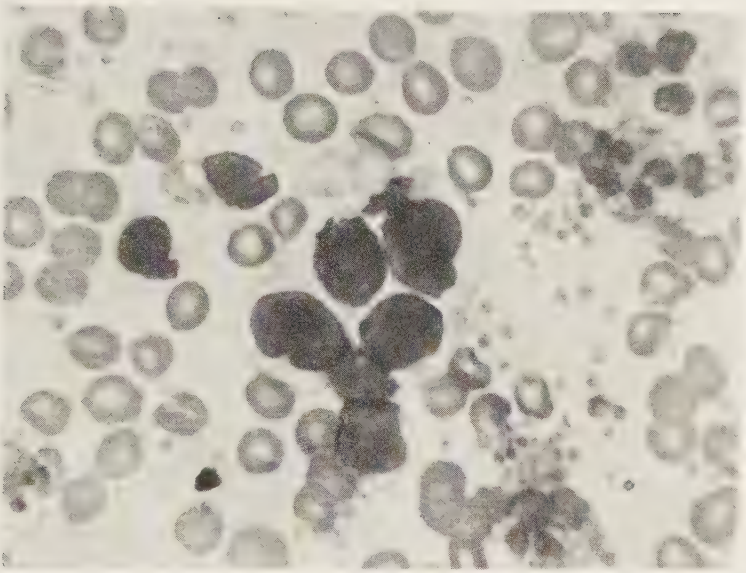

FIG. 4.

Diagnosis.—The diagnostic cells are found most conveniently in the blood but there is no reason why imprints from a skin biopsy should not be used for cytological examination. Alderson *et al.* (1955) have demonstrated the cell in lymph nodes. In our Case 1 as in others previously reported, sternal puncture showed that the characteristic cells were no more numerous in the marrow than could be explained by the presence of blood in the aspirate. Again in our first case as in others, Sézary cells could be found quite readily in an ordinary blood film, but in our second case even when the skin lesions were well established, the first blood film was negative on initial examination. It was only on examination of the buffy-coat smears from the haematocrit at a later date that Sézary cells were seen. A review of the initial ordinary blood film showed one Sézary cell. It is thus evident that if the earliest possible diagnosis is to be made and if indeed the cases with minimal shedding of Sézary cells into the blood are to be revealed, examination of the buffy coat is essential. A description of the technique is given by Goodall (1957).

Certain other cells must be distinguished. The lymphoblast, myeloblast and monoblast can be differentiated by the more primitive character of their nuclei and the more frequent presence of nucleoli. The peroxidase reaction may also be helpful in identifying the last two. The irritation lymphocyte quite frequently has coarsely condensed chromatin not unlike the Sézary cell but such condensations in irritation lymphocytes are always accompanied by intense basophilia of the cytoplasm. The main distinctive features of the ordinary monocyte are its obvious strands of chromatin and fine granularity of

the cytoplasm : sometimes these cells are very similar to the finely granular cells seen in Sézary's Syndrome. For this reason we consider that only cells devoid of granules should be classified as diagnostic of Sézary's Syndrome. The Reed-Sternberg cells of Hodgkin's disease have typically large prominent nucleoli. Megakaryocytes are occasionally seen in blood and buffy-coat films, but they are usually seen there as a nucleus devoid of cytoplasm and when cytoplasm is present, it is obviously granular. Lever (1954) mentions the presence of immature monocytes or lymphocytes in the blood of cases of mycosis fungoides. From examination of the literature we are left in some doubt as to the exact identity of such cells. Allen (1954) has raised the question of whether Sézary's syndrome is in fact mycosis fungoides with invasion of the blood. At present there is scarcely enough evidence to support or refute this hypothesis, but thus far no case of Sézary's syndrome has developed the typical tumours of late mycosis fungoides. In fact the prognosis may be better in Sézary's syndrome than in other reticuloendothelial neoplasms of the skin. We suspect, however,that it is only with the strictest criteria for identification of the abnormal cells that these questions can be correctly answered.

Cytogenesis of the Sézary cell.—It is probable that the Sézary cells originate in the skin, because of their paucity in the marrow and other internal organs. In view of the superficial resemblance of the dermal and epidermal infiltrate to junctional naevoid change and the slight cytological resemblance of the Sézary cell to malignant neuroblasts, in smears, the possibility of a neural origin was raised. The dopa reaction was tested on blood films and sections of skin. In the former the polymorphs were strongly positive and a small proportion of mononuclear cells weakly positive. Unfortunately, after the incubation it was impossible to distinguish whether these weakly positive cells were Sézary cells or ordinary monocytes. In the dermal infiltrate a small amount of pigment was generated, but we cannot exclude the possibility that this was due to the presence of a few scattered polymorphs. In sum, there is not enough evidence to establish a neuro-ectodermal origin for the Sézary cell.

As previous workers have suggested, it is most probable that the Sézary cell arises from the lympho-reticular system. Support for this view is found in both our cases, particularly in the morphology of the blood. As well as the typical monocytoid cells described above, both cases show smaller binucleate and very occasional trinucleate forms in which the nuclei resemble those of lymphocytes. It would appear most likely that the first stage in the development towards the Sézary cell is a nuclear division of a lympho-reticular cell without cytoplasmic division. We think the next stage is fusion of these small nuclei to form a large nucleus which later undergoes condensation of chromatin to to become the typical cerebriform cell. This idea is supported by the Feulgen reaction after which the Sézary cells show practically twice the amount of nuclear staining as the lymphatic cells which accompany them.

Treatment.—In the present state of our knowledge of the disorder, we cannot hope to cure : thus palliation with alleviation of the intense pruritus appears the only sensible measure. As is recorded in our two case reports, both low dosage wide field radiotherapy and steroid therapy (prednisolone) are useful. Dosage and duration of treatment must to a large extent depend on the response of the individual case. One must also bear in mind the general health of the patient, as for example in our second case the benefits of prednisolone lessening the pruritus had to be balanced against its diabetogenic propensity. We consider that intensive radiotherapy or heroic chemotherapy with the radiomimetic or cytotoxic drugs at present available, might well be more damaging to the haemopoietic system than to the Sézary cells. There is, however, one important fact about the disease which distinguishes it from other reticuloendothelial neoplasms and should be kept in mind in the search for a more satisfactory form of treatment. This is that in Sézary's syndrome the proliferative disorder is mainly intradermal without much evidence that metastatic visceral tumours are likely to form. There is thus a slender hope that a chemical or radiochemical agent applied to the skin might have more effect on the course of the disease than systemic therapeutic agents. With this possibility in mind, we tried the effect of local applications of hydrocortisone but without significant effect. In fact, this treatment was no improvement on that with simple antipruritic preparations.

Summary.

1. Two cases of Sézary's syndrome are described.

2. The identity of the Sézary cell is discussed.

3. Microscopical examination of the buffy coat from the haematocrit is the most reliable method of finding the characteristic cell.

4. The origin of the Sézary cell is probably the lympho-reticular tissue of the skin.

5. Treatment is at present palliative.

We are indebted to Dr. J. Kinnear and Dr. J. Rogers for permission to publish these cases and to them and Professor A. C. Lendrum for their help with this work. R. A. Main is a Fellow of the Scottish Hospital Endowment Research Trust.

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DERMATOMYOSITIS PRESENTING AS APLASTIC ANAEMIA.

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This is a brief account of a case of dermatomyositis presenting as aplastic anaemia. We have been unable to find reports of a similar case. It could be argued that the association was purely coincidental, but both diseases are rare and we feel from the time intervals in our case that they were related.

Case Report.

A boilerman, aged 53 years, was admitted to hospital as a medical emergency on account of excessive pallor, epistaxis and muscle cramp. He was perfectly fit until a year and a half previously when he first had attacks of cramp especially in the arms and feet and across the abdomen. Any muscle ached when in use. The attacks of cramp worsened and were later associated with loss of power and shortly before admission he had to come downstairs backwards. For the five days before admission the cramps had been fairly continuous, he had frequent nose bleeds and had passed blood *per rectum* on three occasions. He did not complain at all of the thickening of his skin which might have been present for about a month. There was no history of "dead fingers" or the ingestion of aspirin or other drugs. His general practitioner confirmed that he had prescribed nothing and the patient denied making purchases from the chemist.

Examination.—The patient was extremely pale and agitated, the pulse was 102/min., temperature 101·8° F. and B.P. 140/90. There was diffuse thickening of the skin over the face, neck, arms, legs and upper part of the trunk, with barely discernible sclerodactylia. There was no sclerodermatous sheen but the skin could not be picked up readily and gave the impression of a solid non-pitting oedema. There was obvious thickening and tenderness with loss of power of the quadraceps muscles and to a lesser degree of the biceps with very early contracture of the latter. Purpura was present in scratch marks on the lower parts of the legs and there was bleeding from gums and nose; Hess's test was positive. The firm edge of the liver could be palpated just below the costal margin but there was no splenomegaly or lymphadenopathy.

Relevant Special Investigations and Progress.—In the peripheral blood there was depression of platelets (5000 per cu. mm.) and white cells (2000 per cu. mm.). The haemoglobin varied between 4·2 g. % and 7·0 g. % and he was given three transfusions. Repeated negative sternal and iliac crest marrow punctures confirmed that there was suppression of red marrow activity for the three months before the patient died. Specialist attention was needed on two occasions to stop nose bleeding. Urinary creatine excretion was raised at 720 and 460 mg./24 hr. There were no changes in the radiographs of chest and gut suggestive of scleroderma. Prednisone seemed to help the patient initially but he gradually deteriorated and died in hospital.

Skin and Muscle Biopsy.—The skin showed broadening of the corium with thickening, homogenization and sclerosis of the collagen bundles. There was also generalized thickening of the walls of one or two arterioles in the subcutaneous fat, but no inflammatory cellular infiltrate.

The muscle showed sclerosis of some muscle bundles with replacement fibrosis but no inflammatory infiltrate.

The appearances were those of dermatomyositis, probably in a late stage.

Post Mortem Examination.—The body was that of a pale slightly oedematous man with large petechiae mainly on the abdomen and considerable ecchymosis over the right patella. There was thickening of the skin in the left subclavicular region and on the left forearm where there was a healed biopsy incision. There was no reddening of the marrow of the sternum to indicate haemopoiesis. The middle third of the femur contained a thin fatty fluid slightly tinged with pink at one end only. The muscles of the body and thigh were brownish and mottled in a manner suggesting fibrosis. The heart (340·0 g.) was dilated. The myocardium was flabby and pale. There were some subintimal haemorrhages in the left coronary artery near its origin but there was no occlusion. There were numerous adhesions over most of the surfaces of both lungs (left, 620·0 g. and right 720·0 g.). Both were grossly oedematous with dryer patches of partial consolidation. Apart from a fibrous band constricting a loop of ileum and some small ecchymoses on the serosal surface of the stomach, no abnormality was found in the oesophagus, stomach or intestines. The liver was pale and weighed 1800 g. The spleen (70·0 g.) was pale and rather soft. The thyroid was pale. The kidneys which together weighed 340·0 g. were pale. There were haemorrhages in both pelvises and numerous small abscesses in the parenchyma into which there had been recent haemorrhages.

The brain (1240 g.) was pale and oedematous with both temporal and cerebellar coning. There was a fairly recent infarct in the left corpus striatum and a fresh haemorrhage 1·5 cm. in diameter in the left occipitoparietal region.

Post Mortem Histology.—The skin showed changes less marked but similar to those seen in the biopsy specimen. The muscle of the thigh showed a large area of collagen replacement. The adjacent muscle bundles showed atrophic changes with some increase in the connective tissue between the muscle fibres. There was also hyaline collagen interwoven between some muscle fibres apparently replacing degenerate fibres. There was gross shrinkage of the majority of surviving muscle fibres which showed widespread loss of striation and waxy degeneration. In some cases the sarcoplasm had entirely vanished leaving empty sarcolemmal tubes and prominent and proliferating sarcolemmal cells. There was no inflammatory infiltrate. The lungs showed scattered fibrosis and some emphysema. The striking feature was that of the masses of fibrin lining and even filling alveoli and alveolar ducts. Some of this was fresh fibrin showing a fibrinoid staining reaction and having fresh red blood corpuscles enmeshed in it. Other fibrin masses were paler and older with no recognizable red blood corpuscles in them but with an occasional nuclear remnant. There was no inflammatory cellular response. The kidneys showed an extensive ascending infection with numerous abscesses. The lesions all contained fresh red blood corpuscles. There was a typical inflammatory response with polymorphs round the lesions.

Sections of femur and sternum confirmed the absence of erythropoietic elements in the bone marrow. The vessels in these bones showed no significant abnormality.

Throughout the sections studied there was no evidence of any hypertensive changes nor lesions typical of periarteritis nodosa. There was however well marked intimal cushioning, especially well seen in the larger arteries in the kidney itself. The significance of these lesions was not apparent. No evidence of lesions usually regarded as typical of any of the collagenoses was found in pancreas, thyroid, myocardium, brain, testis, adrenal, spleen, liver or pituitary.

Discussion.

The dermatological differential diagnosis lay between dermatomyositis and scleroderma. The presence of pain in joints and muscles, early contractures, absence of a history of preceding illness and subsequent lack of resolution tends to exclude scleroedema adultorum. O'Leary (1949) has commented on the difficulty some times experienced in separating dermatomyositis and scleroderma even with histopathological studies, though he mentions that the hidebound change usually comes first in scleroderma.

In our patient, muscle symptoms developed one and a half years before skin changes were noticed and furthermore his main complaint was of cramps, as distinct from rheumatic joint pain. This is clinically in favour of dermatomyositis. The pathological changes confirmed this view as the skin and muscle were the tissues mainly affected (Dowling, 1955). The histological picture of the lungs, though not specific, has been commented on before by other authors discussing viscerocutaneous collagenoses (Pagel and Triep, 1955). In these lesions there was no cellular inflammatory infiltrate, though polymorphs were present in the inflammatory lesions in the kidneys. The absence of cellular infiltrate in the lesions of dermatomyositis was therefore not a manifestation of the aplastic anaemia but an indication that the pathological process was either naturally quiescent or suppressed by the steroid treatment. Both the dermatomyositis and the aplastic anaemia must have contributed to his death.

Though this is the first report specifically drawing attention to a case in which both dermatomyositis and aplastic anaemia have been found, Beerman (1948) refers to aplastic anaemia occurring in scleroderma and one of the cases of dermatomyositis reported by Pagel *et al.* (1949) was found at autopsy to have aplastic anaemia. We feel that this is more than a coincidence as both conditions are rarities ; furthermore the clinical progress of the case with aplastic anaemia presenting after the onset of dermatomyositis supports the contention that the anaemia was a complication of the latter.

Summary.

A case of dermatomyositis presenting as aplastic anaemia is described and details of the pathological findings are given. The authors are able to offer only indirect evidence that the two disease processes are related.

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DARIER'S DISEASE AND HAEMOGLOBIN H THALASSAEMIA IN A CHINESE.

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Darier's disease is a rare skin disorder characterized by a symmetrical fairly well generalized eruption of small firm papules which become crusted over and by coalescence produce papillomatous, vegetating and tumour-like growths. Two or more cases can occur in the same family (Hitch *et al.*, 1941 ; Counter, 1954). Its aetiology is unknown, but it is considered by some to be a manifestation of vitamin A deficiency, due either to hereditary or acquired impairment in the absorption of vitamin A or in the conversion of provitamin A to vitamin A (Peck, Glick, Sobotka and Chargin, 1943).

Haemoglobin H was first demonstrated by the technique of electrophoresis in patients suffering from hypochromic microcytic anaemia resistant to therapy, with splenomegaly and a blood picture indistinguishable from that of thalassaemia (Gouttas, Fessas, Tsevrenis and Xefteri, 1955 ; Rigas, Kolar and Osgood, 1955). This haemoglobin is identified by its characteristic properties on electrophoresis at alkaline and acid reactions and by the production of intra-erythrocytic inclusion bodies on supra-vital staining with brilliant cresyl blue. During the last two years, twenty-nine cases have been detected in Singapore and Malaya, mainly in Chinese but also in Malays and Nepalese Gurkhas (F.V.).

The case is here presented of a Chinese man suffering from Darier's disease in whom investigation of a persistent, therapy-resistant anaemia revealed the presence of haemoglobin H thalassaemia.

Case Report.

A Chinese man, aged 40, first noticed small nodular thickenings of the skin at the back of his head when he was about 9 years old. The skin condition remained quiescent till he was 14 years old when it started on the face. Gradually the eruption spread to the trunk and limbs.

When first seen in 1949, at the age of 31, he was in good health. The eruption involved the face, front of the trunk, and the limbs. The eruption was symmetrical and consisted of prominent hair follicles filled with horny plugs which tended to become confluent, producing thick, dark grey, greasy, raised plaques. On either side of the nose, these plaques were heaped up into two nodules. The oral mucosa was not involved. On the body, the lesions were profuse on the front and thickest in the groins and pubic region (Fig. 1). The back was relatively free except for the

Fig. 1.

neck, the interscapular area and along the spine. On the upper limbs they were most numerous on the extensor surface and the palms were not affected, while on the lower limbs they were confined to the legs below the knees, without affecting the soles of the feet. Occasionally the affected areas cracked and oozed a serous fluid which produced a pungent offensive odour. A diagnosis of Darier's disease was made. A biopsy specimen from a lesion on the right leg was examined by Dr. Shanmugaratnam of the Pathology Department of the General Hospital, Singapore. He reported "marked hyperkeratosis associated with the formation of keratotic plugs which do not have any demonstrable relationship to pilosebaceous follicles. Irregular acanthosis is present and there are widespread intraepidermal lacunae projecting into which are the so-called 'villi' or elongated and tortuous papillae lined by a layer of basal cells. There are striking dyskeratotic changes represented by a few '*corps ronds*' and a large number of '*grains*' which are found at all levels of the epidermis and lying loose in the lacunae. Associated with these changes there are areas of parakeratosis where the granular layer is diminished or absent. The dermis exhibits a mild nonspecific chronic inflammatory reaction. The histological features are characteristic of Darier's disease." Vitamin A therapy was instituted: 100,000 i.u. daily by injection for two weeks and 100,000 i.u. daily by mouth for three months. This was followed by intramuscular ACTH 25 mg. every six hours for three weeks. However, there was no improvement.

In 1954 he was admitted to hospital for Ludwig's angina caused by several septic teeth. This was effectively treated with penicillin and extraction of the affected teeth. The liver and spleen were found to be enlarged to three fingers' breadths below the costal margins. The haemoglobin content of his blood was 6·0 g. %, and the red cells numbered 2·0 million per cu. mm. The peripheral blood showed hypochromia,

anisocytosis, poikilocytosis and target cells, with occasional late normoblasts and giant forms of platelets. The bone marrow showed considerable erythroid hyperplasia affecting mainly the intermediate normoblasts. Megakaryocytes were increased in number, and the erythroid : myeloid ratio was 1 : 2·2. The anaemia and hepatosplenomegaly were attributed to hypersplenism. Several months of oral and parenteral iron therapy produced no improvement in the anaemia. The lesions on the forearms were scraped with a scalpel and sandpapered ; those on the legs were excised and full thickness skin was grafted from normal looking areas on the thighs. The grafts took well, but the keratosis recurred in the sandpapered areas. Sandpapering of various regions was performed during subsequent visits.

In 1958 he was admitted for reinvestigation of his anaemia. His skin condition was unchanged. He was pale but not jaundiced. The liver and spleen were palpable three fingers' breadths below the costal margins and were firm.

Investigations.—Hb. 8·0 g. %. R.B.C. 3·5 million per cu. mm., P.C.V. 38%, M.C.H.C. 21%, M.C.V. 107 cu. μ platelets 40,000 per cu. mm., reticulocytes 3%. Peripheral blood showed hypochromia, marked anisocytosis and poikilocytosis. Target cells 3%. In the osmotic fragility test haemolysis started at 0·45% sodium chloride and was complete at 0·2%. Serum bilirubin 0·3 mg. %. Stools : no ova present. Skiagrams of the chest, skull and hands were normal. On paper electrophoresis at pH 8·6 and 6·5, the haemoglobin was found to be a mixture of haemoglobins A (approximately 80%) and H (approximately 20%). One minute alkali denaturation test 4·5%. On supra-vital staining of the blood with brilliant cresyl blue (Gouttas *et al.*, 1955) nearly all of the erythrocytes were noted to contain multiple small dark blue inclusion bodies.

Family History.—The patient is the eldest of his generation in the family and is single. Both his parents are living and he has two younger sisters and two younger brothers. There is no history of similar skin disease in the family including the grandparents. Only his father was examined : his haemoglobin was 15 g. % and electrophoretic studies showed only normal adult haemoglobin.

Discussion.

The presence of haemoglobin H in the circulating erythrocytes is a hereditary characteristic which appears to require the simultaneous inheritance of a gene for thalassaemia and a gene for the abnormal haemoglobin (Motulsky, 1956). The blood picture in the present case is similar to that of thalassaemia. It was unfortunate that other members of his family were not available for investigation.

According to Becker and Obermayer (1947), Darier's disease is familial in 25 to 50% of cases. It has not been possible to show a family incidence in this case. Darier's disease is rare and in 6431 cases of skin diseases seen in Singapore in 1953, only one case of Darier's disease was found (Khoo, 1953). The improvement in many cases, though not in all, produced by massive and prolonged vitamin A therapy together with the findings of Peck and associates (1941 ; 1943) seem to indicate a hereditary or acquired failure of absorption of this vitamin or of its formation from provitamin A substances in the diet. No noticeable response was produced by vitamin A therapy in the present case. It is interesting that skin grafts from normal donor areas prevented recurrence of the lesion.

It is unlikely that the blood condition adversely affected the skin disorder, though it is possible that the " stress " of Darier's disease unmasked what might otherwise have been a mild haematological state in this patient. In six of the cases of haemoglobin H thalassaemia so far detected in Singapore, the anaemia was first noted in association with pregnancy and improved spontaneously after delivery. One of these cases has been reported (Brain and Vella, 1958). In another case in a girl aged eight years, the anaemia was first noted in association with tuberculosis of the spine. It is possible that " stress " may be required to make clinically manifest some cases of haemoglobin H thalassaemia.

Summary.

The case is presented of a Chinese man suffering from Darier's disease and haemoglobin H thalassaemia.

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SERUM PROTEINS IN SKIN DISEASE.

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Serum protein levels have frequently been reported in individual skin diseases (Mulvehill, 1944; Robert, 1948; Beek, 1949; Leinbrock, 1952; Röckl and Jaroschka, 1952; Funk *et al.*, 1952 and many others). However, many of these reports are little more than anecdotal. Frequently only two or three cases of a particular disease have been studied and very rarely has any statistical analysis of results been attempted.

We have estimated the serum proteins of selected patients under treatment at St. John's Hospital for Diseases of the Skin for the past three years and have fractionated over eight hundred specimens using the technique of paper electrophoresis. Some of our results are reported and analysed here.

Material.

We analysed serum from 27 normal subjects—laboratory workers, nurses, cleaners and porters, ranging in age from 20 to 60 years. We also examined specimens from the following cases.

Atopic eczema	17	cases
Eczema	35	,,
Disseminated lupus erythematosus	19	,,
Discoid ,, ,,	38	,,
Seborrhoeic dermatitis	5	,,
Scleroderma	8	,,
Lichen planus	7	,,
Pemphigoid	10	,,
Pemphigus vulgaris	11	,,
Pemphigus foliaceus	4	,,
Exfoliative dermatitis	32	,,
Dermatitis herpetiformis	4	,,
Psoriasis	71	,,
Photosensitivity	16	,,

The cases of psoriasis and discoid lupus erythematosus probably represented a fair sample of patients attending this hospital for these conditions. A relatively large proportion of the remainder were in-patients, and presumably more

severe examples of the conditions in question. All our cases of seborrhoeic dermatitis, for example, were severe enough to require admission to hospital.

Methods.

We measured total protein by the biuret method of Wolfson, Cohn, Calvary and Ichiba (1948). For our standard in this test we used the freeze-dried serum prepared by Glaxo Laboratories and analysed by a joint committee of the Association of Clinical Pathologists and the Association of Clinical Biochemists. The standard derived from this serum was measured when each batch of sera was analysed.

The serum proteins were broken into fractions by electrophoresis on Whatman No. 1 paper (for chromatography) essentially by the method of Jencks, Jetton and Durrum (1955), modified by using the EEL bath which requires the paper to lie horizontally. The fixed strip, stained with bromophenol blue and cleared with liquid paraffin, was scanned in the EEL scanner and the individual fractions (represented by the tracing so obtained) were measured by cutting out individual curves and weighing them.

Results.

These are shown in Tables I to III and Figs. 1 to 14. Table I shows the results of six analyses of a single sample of serum.

Table I.—*Results of Six Analyses of a Single Specimen of Serum.*

Analysis No.	Albumin, g.%.	Globulins, g.%.			
		α_1	α_2	β	γ
1	3·5	0·3	0·9	1·1	1·2
2	3·5	0·3	0·8	1·1	1·2
3	3·5	0·3	0·7	1·0	1·5
4	3·4	0·3	0·8	1·1	1·4
5	3·3	0·3	0·8	1·2	1·4
6	3·4	0·4	0·9	1·0	1·4

Total proteins 7·0%

Table II shows the values found in 27 normal individuals.

Table II.—*Serum proteins in 27 Normal Individuals.*

	Total	Albumin, g.%.	Globulins, g.%.			
			α_1	α_2	β	γ
Mean	6.80	4·14	0·225	0·550	0·727	1·104
S.D.	0.355	0·383	0·079	0·132	0·110	0·247
Range (i.e. mean ± 2 S.D.),	6·1–7·5	3·4–4·9	0·1–0·4	0·3–0·8	0·5–0·9	0·6–1·6

Both tables are self-explanatory. Figs. 1 to 14 show the results obtained in various skin diseases. The height of the shaded column in these is proportional to the mean value of the particular protein fraction in the skin disease in question. Beside this, for comparison, is a column, the height of which represents the normal value of the fraction. For convenience, the individual globulin fractions are represented on a larger scale than the total albumin and combined globulins. Below the columns are three figures—*M*, the mean value of the

protein or protein fraction in grams per cent, S, the standard deviation of observed values about the mean and P, the probability, derived from Student's "t" test that the difference between normal and pathological means was due to chance. Following the usual custom, we regard as significant any difference where P is less than 0·05 and in such cases an asterisk appears at the top of the column. The number in brackets at the top of each Figure is the number of cases analysed.

To the clinician, it is of less immediate interest to know whether two groups show differences between each other than the likelihood that an individual patient will show some particular abnormality. Table III shows the percentages of patients who showed the specified abnormality of the serum proteins.

TABLE III.—*Percentage of Patients Showing Specified Abnormality.*

Skin condition.	Total protein		Albumin lowered	Globulin fraction raised			
	Raised	Lowered		α_1	α_2	β	γ
Psoriasis	1	23	18	4	8	25	4
Eczema	3	14	43	14	23	29	23
Exfoliative dermatitis	0	38	69	6	6	19	16
Atopic dermatitis	6	0	24	6	18	18	18
Photosensitivity	6	18	13	0	13	13	19
Seborrhoeic dermatitis	40	0	0	20	20	40	40
Lichen planus	14	0	14	0	14	29	0
Dermatitis herpetiformis	0	25	50	25	25	25	25
Pemphigoid	0	70	70	0	0	10	10
Pemphigus vulgaris	0	73	91	27	35	9	9
Pemphigus foliaceus	0	50	25	0	25	25	0
Discoid lupus erythematosus	5	13	3	3	3	16	10
Systemic lupus erythematosus	27	0	27	0	27	33	88
Scleroderma	13	38	50	0	13	63	13

Two further points are worthy of note. Cryoglobulins were found in two cases of systemic lupus erythematosus and in two of three cases of Gougerot's *maladie trisymptomatique*. Two cases of systemic lupus erythematosus with markedly affected kidneys had a very different protein pattern from the other 17 cases of this disease and are not included in the statistical analysis of Fig. 13. The results of these are seen in Table IV.

TABLE IV.—*Serum Proteins in g.% of 2 Cases of Disseminated Lupus Erythematosus with Marked Renal Involvement.*

Case.	Total.	Albumin.	Globulins.			
			α_1	α_2	β	γ
1	4·0	1·8	0·2	0·8	0·5	0·7
2	4·7	2·4	0·4	0·9	0·3	0·7

Case 2 showed cryoglobulinaemia.

Both showed very low total protein and low albumin: β- and γ-globulin fractions were lowered and the α_1- and α_2-fractions raised.

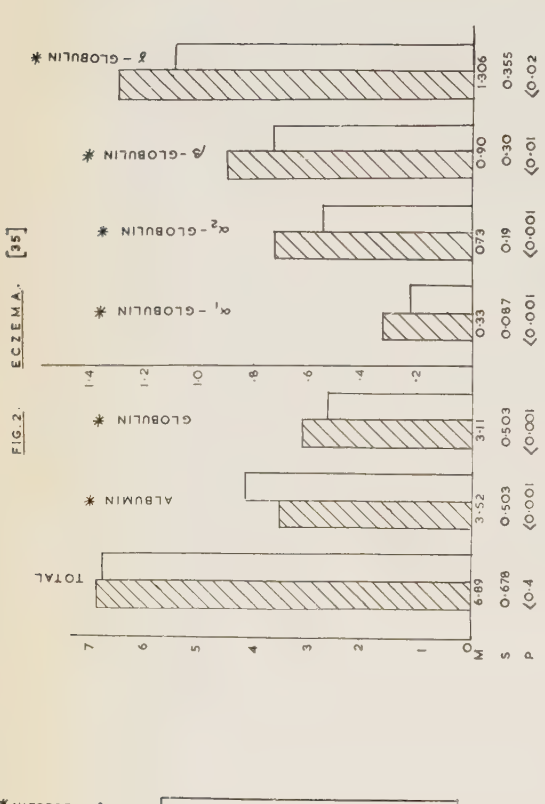


FIG. 2. ECZEMA. [35]
TOTAL
ALBUMIN
GLOBULIN
α1 - GLOBULIN
α2 - GLOBULIN
β - GLOBULIN
γ - GLOBULIN
M 6·69 3·52 3·11 0·33 0·73 0·90 1·306
S 0·678 0·503 0·503 0·087 0·19 0·30 0·355
P <0·4 <0·001 <0·001 <0·001 <0·001 <0·01 <0·02

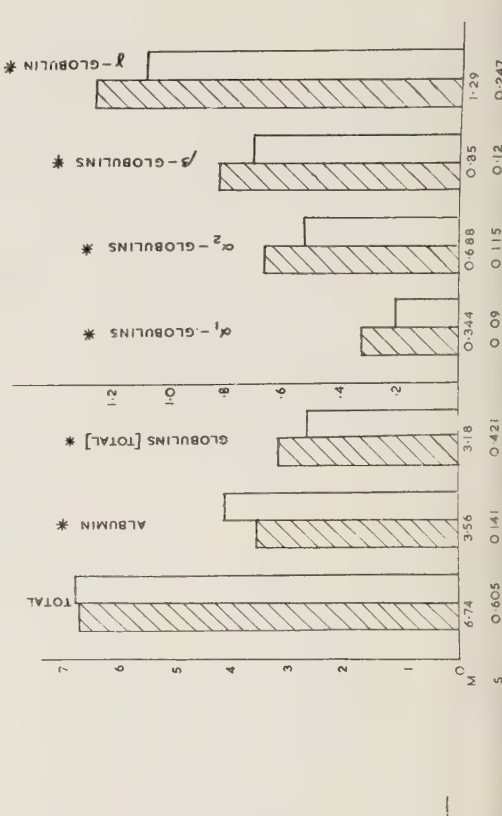


FIG. 4. ATOPIC ECZEMA [17]
TOTAL
ALBUMIN
GLOBULINS [TOTAL]
α1 - GLOBULINS
α2 - GLOBULINS
β - GLOBULINS
γ - GLOBULIN
M 6·74 3·56 3·18 0·344 0·688 0·85 1·29
S 0·605 0·141 0·421 0·09 0·115 0·12 0·247
P <0·01 <0·001

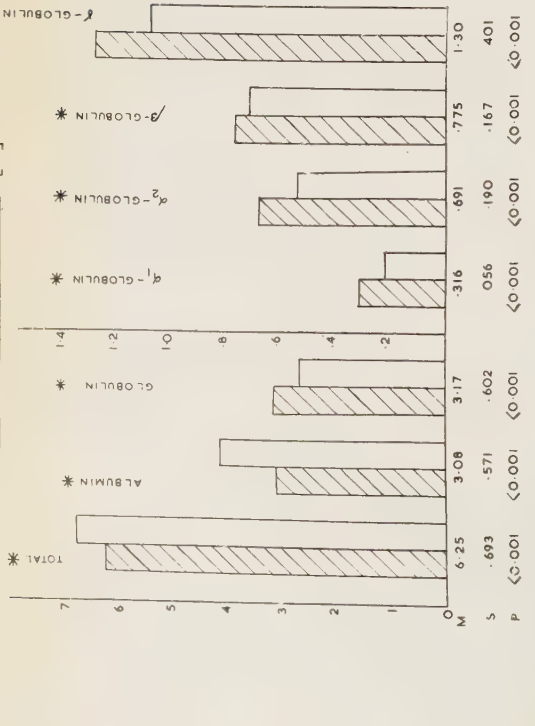


FIG 3. EXFOLIATIVE DERMATITIS [32]
TOTAL
ALBUMIN
GLOBULIN
α1 - GLOBULIN
α2 - GLOBULIN
β - GLOBULIN
γ - GLOBULIN
M 6·25 3·08 3·17 ·316 ·691 ·775 1·30
S ·693 ·571 ·602 056 190 ·167 401
P <0·001 <0·001 <0·001 <0·001 <0·001 <0·001 <0·001

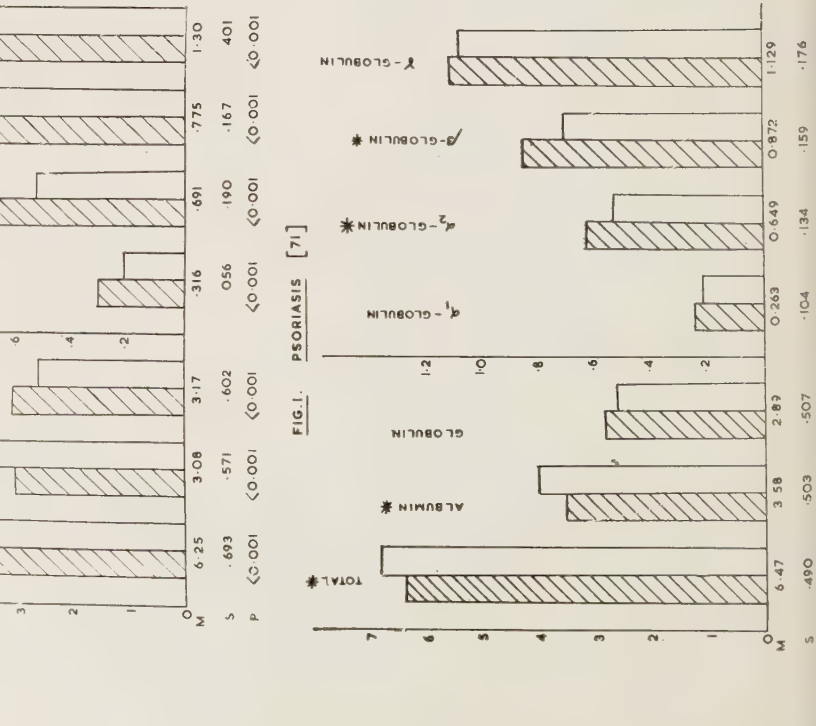


FIG. 1. PSORIASIS [71]
TOTAL
ALBUMIN
GLOBULIN
α1 - GLOBULIN
α2 - GLOBULIN
β - GLOBULIN
γ - GLOBULIN
M 6·47 3·58 2·89 0·263 0·649 0·872 1·129
S ·490 ·503 ·507 ·104 ·134 ·159 ·176
P <0·001 <0·001 <0·2 <0·1 <0·001 <0·001 <0·7

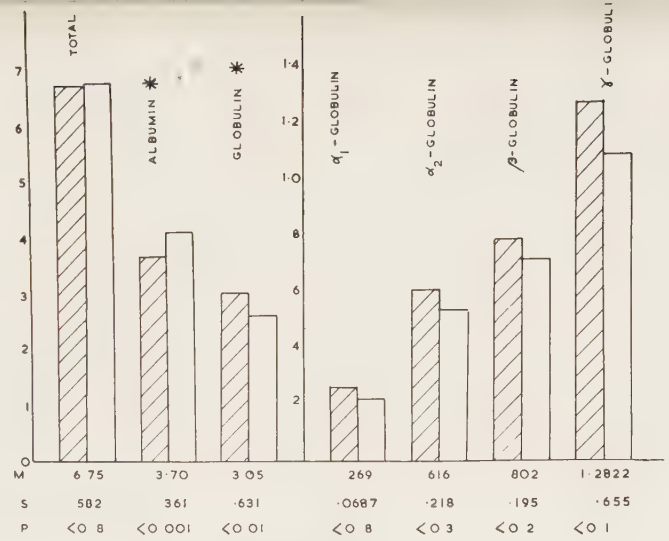
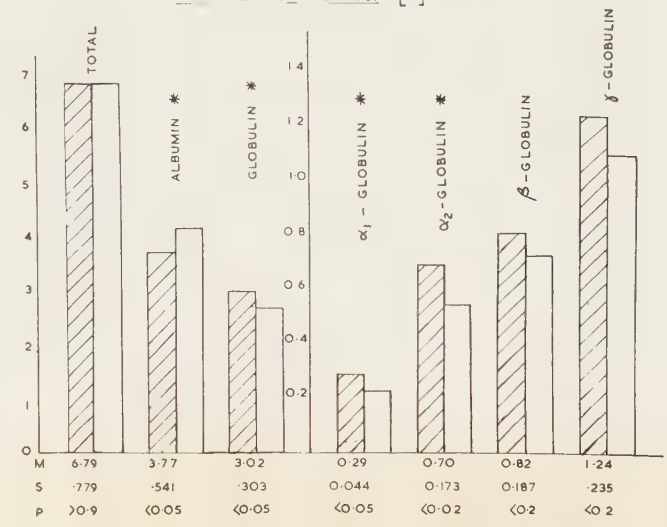


FIG. 7. LICHEN PLANUS. [7]



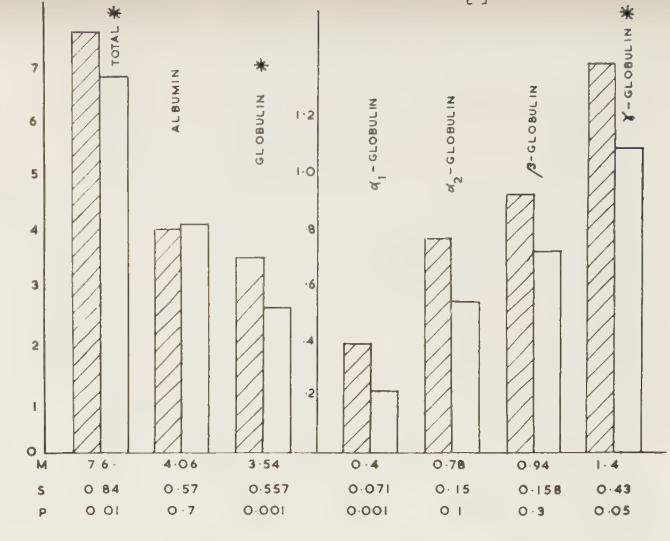


FIG. 8. DERMATITIS HERPETIFORMIS [4]

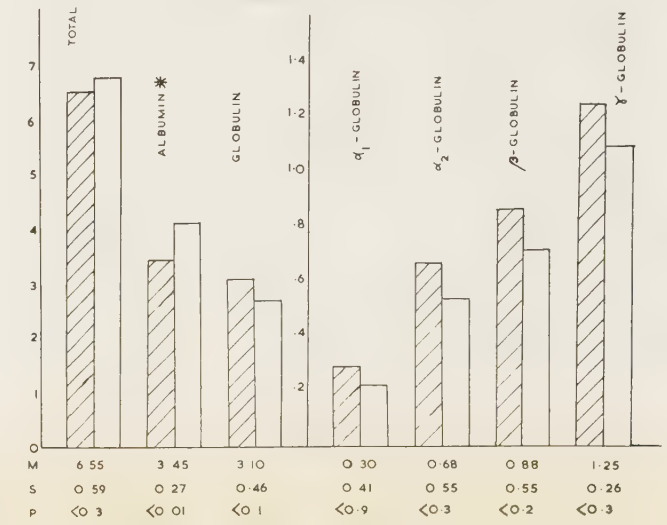


FIG. 9. PEMPHIGOID [10]

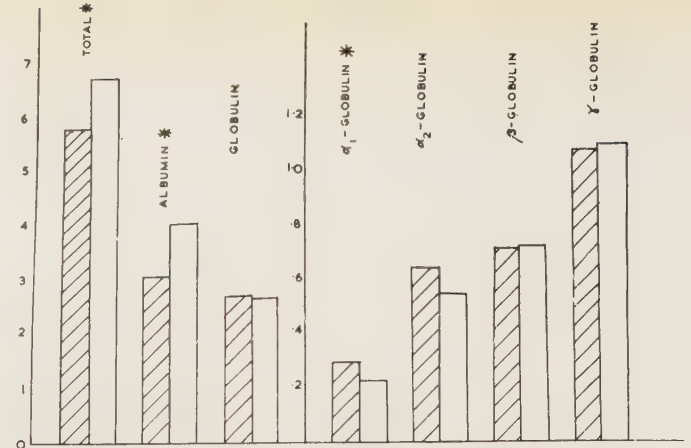


FIG 10. PEMPHIGUS VULGARIS [11]

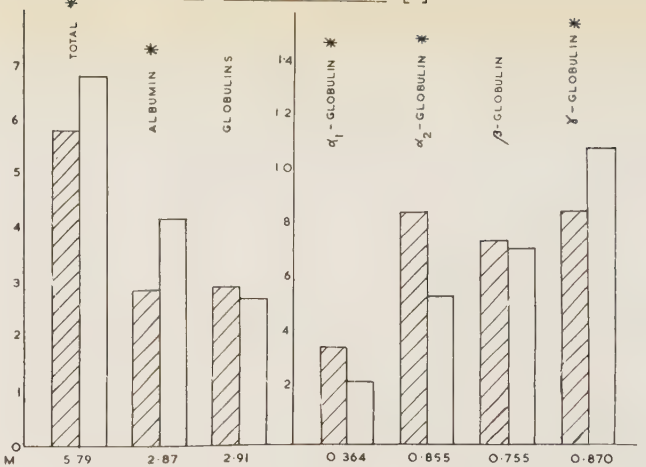


FIG 11. PEMPHIGUS FOLIACEOUS [4]

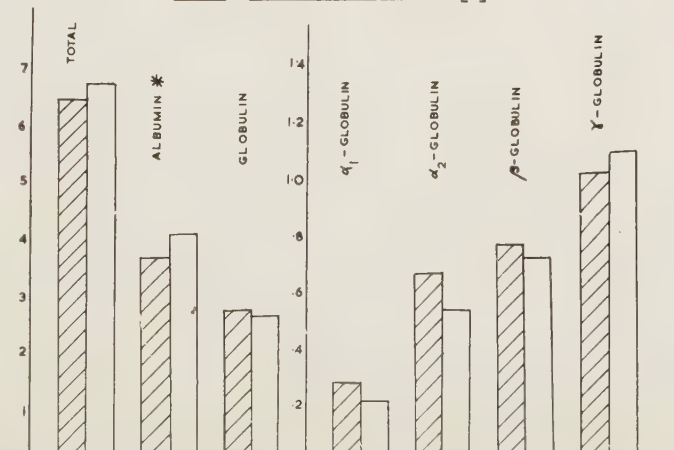
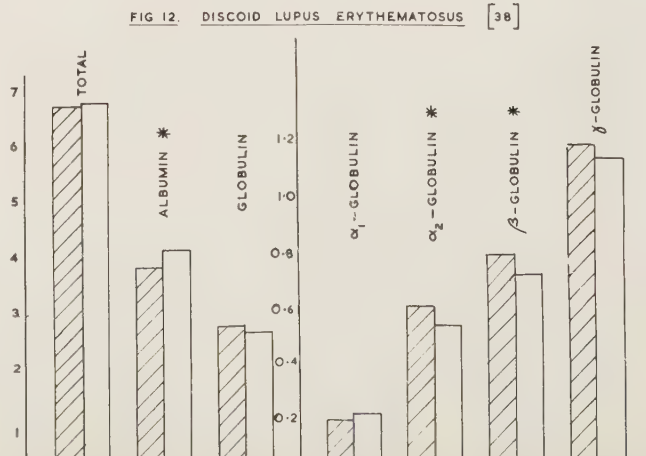


FIG 12. DISCOID LUPUS ERYTHEMATOSUS [38]



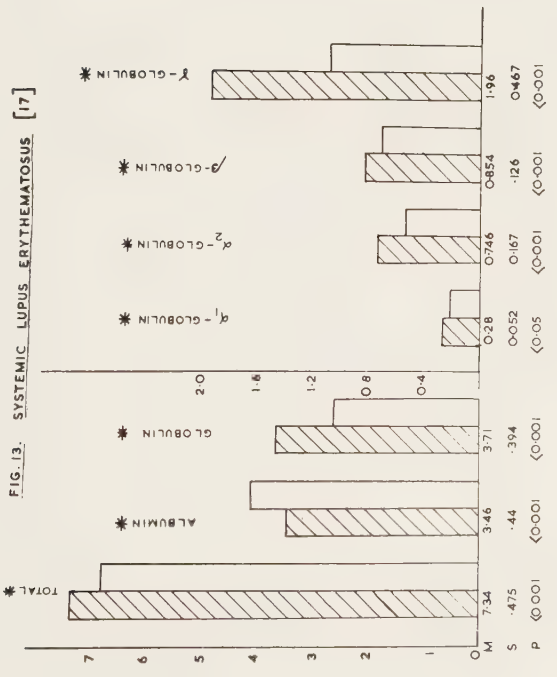


FIG. 13. SYSTEMIC LUPUS ERYTHEMATOSUS [17]

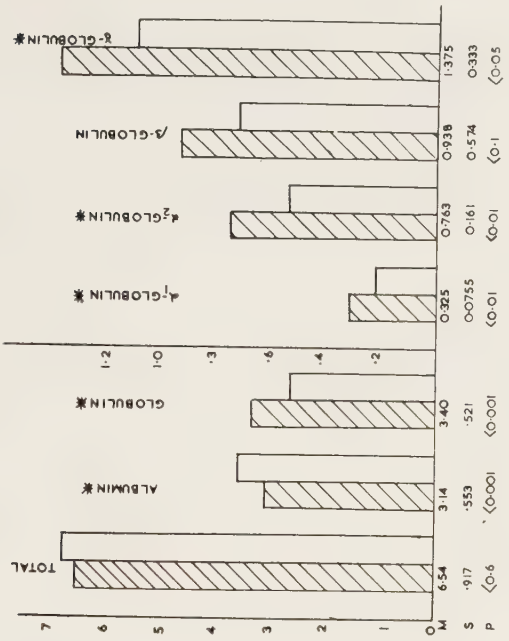


FIG. 14. SCLERODERMA [7]

Discussion.

The validity of paper electrophoresis for quantitative assay of albumin and globulin fractions requires some justification. As Jencks, Jetton and Durrum have shown, scrupulous care in carrying out this technique leads to reproducible results comparable to those obtained by electrophoresis in free solution, except that "tailing" of albumin on paper and the lack of applicability of Beer's law to the scanned stained paper lead to lower values for albumin. This objection is not serious if two groups are being compared, provided that the actual quantity of serum applied to the paper is carefully standardised. Although when serum albumin is low, tailing is relatively greater, the error caused by non-observance of Beer's law is relatively less, so that the two sources of error tend to cancel out. We note that our normal figures lie within the range quoted by Owen (1958) as having been found by several other groups of workers using techniques allied to ours.

Our most striking finding is that every skin disease studied shows some significant abnormality of at least one protein fraction. When groups of cases are considered, various protein fractions may be affected, but as far as individual cases are concerned, a pattern is hard to find (cf. Table III) except in the following conditions.

(i) *Exfoliative dermatitis.* Low total protein is common and low serum albumin the rule.

(ii) *Pemphigoid and pemphigus vulgaris.* These have such outstanding abnormalities that a tentative diagnosis can frequently be made merely by looking at the stained electrophoretic strip. Low albumin and relatively raised globulins are usually seen. Differences are found between pemphigoid and pemphigus vulgaris. In the latter there is frequently an absolute rise in α-globulin fractions which is not seen in pemphigoid. Also, there is a tendency for the γ-globulin to be in the low normal range. Thus 73% of cases of pemphigus vulgaris have a γ-globulin of less than 1g.% contrasted with 50% of cases of pemphigoid and 33% of normal subjects.

(iii) *Systemic and discoid lupus erythematosus.* As might be expected, 88% of cases of systemic L.E. have raised γ-globulin, compared with only 10% of cases of discoid L.E. In some cases, therefore, the presence or absence of raised γ-globulin may be of help in differentiating between these two conditions.

Summary.

1. The results of analysis of the serum protein of 27 normal individuals and of 277 cases of skin disease are described and discussed.

2. All the cases of skin disease showed statistically significant abnormalities in at least one protein fraction.

3. However, of the skin diseases mentioned in this paper, abnormalities in an individual case will only be seen frequently in the following.

(i) Exfoliative dermatitis—low total protein and low albumin.

(ii) Pemphigoid—low total protein, low albumin, relatively raised α-globulins.

(iii) Pemphigus vulgaris—low total protein, low albumin, absolutely raised α-globulins, relatively low γ-globulins.

(iv) Systemic lupus erythematosus—markedly raised γ-globulin, often associated with raised total protein.

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FAMILIAL LUPUS ERYTHEMATOSUS.

A Report of Two Cases.

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Since Sequeira (1903) described lupus erythematosus in two sisters, forty further examples with a familial background have been reported. The majority had the discoid form. In only eight families was there evidence of systemic involvement and these have been reviewed by Leonhardt (1957). This author added a further family in which three members out of eight with hypergammaglobulinaemia had systemic lupus eruthematosus.

Although Kaposi (1872) first suggested a relationship between the discoid and systemic forms of lupus erythematosus, there is still no agreement that they are forms of the same disease. There are many experienced dermatologists and general physicians who believe that the two diseases are distinct, or have never seen the discoid form develop into the systemic (Reiches, 1957). Reiches himself disagrees with the latter view, as do Cohen and Cadman (1953), Harvey *et al.* (1954) and Marten and Blackburn (1956) who believe that the division is artificial, that the disease categories often overlap and that discoid lupus erythematosus may progress into systemic lupus erythematosus. The view of the majority appears to be that the two diseases are closely related.

The following case reports describe a mother and daughter with lupus erythematosus and show certain unusual features, in particular the clinical dissimilarity of the two cases, contrasting with previously published reports.

Case Reports.

Case 1. In 1948, at the age of 32, Mrs. R. M. attended St. John's Hospital for Diseases of the Skin, London, under Dr. A. D. Porter, with the typical rash of discoid lupus erythematosus confined to the face. In 1950, the rash became disseminated over the trunk and limbs and she was admitted to the Bethnal Green Hospital under Dr. M. C. Ashton. Apart from the rash and a temperature of 99·4° F., she showed no abnormality on clinical examination.

Investigations 1950.—Hb. 64%, R.B.C's. 4,320,000 per cu.mm., W.B.C's. 9,400 per cu.mm. with a normal differential, E.S.R. 69 mm./hr., proteinuria with large numbers of red blood cells in deposit, serum albumin 3·4 g./100 ml., serum globulin 3·8 g./100 ml., W.R. negative. The abnormal results suggested some systemic involvement.

Following this episode, she returned to the out-patient care of St. John's and was given mepacrine 100 mg. daily. The lesions cleared leaving only scars on the face and she was discharged in 1956 virtually cured.

In 1958, when we saw her at the Royal Free Hospital, she felt well and the skin lesions were still inactive.

Investigations 1958.—No. L.E. cells in the serum, E.S.R. 20 mm./hr., haemoglobin and white cell count normal, serum albumin 4·2 g./100 ml., serum globulin 3·8 g./100 ml., electrophoretic strip—a slight increase of γ-globulin, no proteinuria. These investigations were essentially normal other than the persistent hypergammaglobulinaemia.

Case 2. Mrs. R. W., aged 61, the mother of Mrs. R. M., was admitted to the Royal Free Hospital in November 1957 with hepatitis. For four weeks she had had general malaise and was observed to be jaundiced by her friends and later by her doctor. Her urine was dark, her motions pale but she had no pruritus, nausea or vomiting. She complained also of pain in her arms, wrists and the right knee which was swollen.

For forty years she had had symptoms of a duodenal ulcer and in 1955 a barium meal at the Royal Free Hospital confirmed the diagnosis. In 1953, she complained of backache, considered to be root pain from spinal osteoarthritis with disc degeneration. In June 1957, she suddenly developed a right-sided hemiplegia with difficulty in speech, which rapidly improved. For her peptic ulcer she had had alkalies, for her back and limb pains simple coal tar analgesics. There was no history of administration of sulphonamides or other complex drugs.

Examination on first admission.—She was mildly jaundiced but had no spider naevi, palmar erythema or rash. The liver was enlarged two fingers' breadths below the right costal margin and was tender. There were minimal signs of right hemiparesis. The blood pressure was 145/80. The heart and lungs showed no abnormality.

Investigations.—W.B.C.'s. 3,600 per cu. mm. (72% neutrophils), serial weekly E.S.R's. 74, 80, 63, 40, 82 and 58 mm./hr. Many L.E. cells were found in the serum on repeated examinations. Sternal marrow: normoblastic maturation with slightly reduced cellularity associated with hypoplasia of the granulocyte series. Liver function tests: Van den Berg; direct positive, total bilirubin 1·5 mg./100 ml., albumin 2·7 g./100 ml., globulin 4·1 g./100 ml., alkaline phosphatase 22 units, thymol turbidity 10 units, thymol flocculation positive, colloidal gold 5 units, zinc sulphate turbidity 10 units, serum transaminase 125 units (normal range 0–20). Electrophoresis confirmed the decrease in albumin and increase in γ-globulin. Liver biopsy suggested the recovery phase of necrotic hepatitis. No proteinuria. The electrocardiogram was normal. The investigations were consistent with hepato-cellular damage and systemic lupus erythematosus.

In hospital she had an irregular fever, of up to 100 F. which gradually settled as did her symptoms and jaundice. Under out-patient supervision, she complained intermittently of pain in the arms, back and upper abdomen with occasional nausea and vomiting. In March 1958, the liver was still enlarged: the serum bilirubin was 0·5 mg./100 ml., serum albumin 3·5 g./100 ml. and globulin 5·0 g./100 ml. The electrophoretic strip showed a gross increase in γ-globulin.

Second admission.—In July 1958, she was readmitted to the Royal Free Hospital with two weeks' history of fever, severe malaise, pleural pain in the left lower chest and loss of weight. Aureomycin prescribed by her general practitioner had had no obvious effect. The pain in the limbs had increased and was associated with stiffness of the joints in the mornings.

Examination.—The breath sounds were diminished on the left side. There was tenderness over the left lower ribs and in the subcostal area. The blood pressure was 190/95 and a precordial systolic murmur was heard. The liver was still enlarged.

Investigations, July/August 1958.—Still showed abnormal hepatocellular tests.

W.B.C's. 4,800 per cu. mm. (81% neutrophils), weekly E.S.R's. 60, 90, 42 and 36 mm./hr. Blood urea 22 mg./100 ml., no proteinuria. Liver function tests : bilirubin 0·4 mg./100 ml., albumin 3·3 g./100 ml., globulin 5·0 g./100 ml., alkaline phosphatase 16 units, thymol turbidity 10 units, thymol flocculation ++ +, colloidal gold 5 units, zinc sulphate 12 units, serum transaminase 45 units. Electrophoresis : gross increase in γ-globulin. L.E. cells present in large numbers in four specimens of blood. Rose's test negative, C-reactive protein +6. Precipitation test for systemic lupus erythematosus globulins positive. Radiograph of chest : obliteration of the left costophrenic angle.

During the first two weeks she had a persistent fever of up to 102° F., unresponsive to further antibiotics, but on steroid therapy she improved steadily, the temperature becoming normal, although a pleural rub was heard.

By September 1958 she had changes resembling early rheumatoid arthritis in her hands with erythema of the nail folds ; following this she began to have severe attacks of Raynaud's phenomenon in both hands.

Discussion.

The occurrence of discoid and subacute lupus erythematosus in mother and daughter supports the concept that they are variants of the same pathological process. The daughter had a predominantly benign cutaneous illness for ten years, with only one episode of dissemination of the skin lesions. The urinary changes present were evanescent and were unlike those of the nephritis of lupus erythematosus which is usually steadily progressive, death occurring in one to five years (Muehrcke *et al.*, 1957). The only other manifestations of systemic activity were the raised sedimentation rate and hypochromic anaemia, which are common findings in discoid lupus erythematosus (Marten and Blackburn, 1956). However iron deficiency anaemia frequently occurs in women in the child-bearing period. This evidence suggests short lived but minimal systemic involvement. Her mother, on the other hand, had systemic lupus erythematosus without cutaneous signs.

In the families reviewed by Leonhardt, the manifestations of lupus erythematosus were clinically similar in the affected relatives and were either predominantly systemic or cutaneous. The exceptions were the two cases reported by McCuistion and Schoch (1954) who described a case of possible discoid lupus erythematosus in a newly born infant, whose mother later developed systemic lupus erythematosus. These authors raised the possibility of some factor being transmitted across the placenta. This has recently been demonstrated by Berlyne *et al.* (1957) who obtained a positive L.E. cell test in the first seven weeks of life in healthy infants born of mothers with systemic lupus erythematosus.

The illness in Case 2 appeared to start with hepatitis, although several months before she had a cerebrovascular accident which may have been related. She appears to belong to that small group of patients who develop systemic lupus erythematosus after hepatitis (Mackay *et al.* 1956 ; Beckett, 1957). It is not clear whether the hepatitis in these patients is a manifestation of systemic

lupus erythematosus or whether virus hepatitis acts as a precipitating factor in a constitutionally predisposed patient.

Both of our patients had hypergamma-globulinaemia ; another daughter has no abnormality of serum proteins. The findings in the family reported by Leonhardt suggested that hypergamma-globulinaemia was the basic inherited abnormality. In the majority of patients it is probably a response to the disease. In the present cases, L.E. cells were demonstrated only in the mother but it is possible that had the test been available in 1950, they might have been found during the cutaneous dissemination during the daughter's illness. These cells can be present in the absence of hypergamma-globulinaemia and *vice-versa* (Harvey, 1954).

With the use of the L.E. cell test, the diagnosis of systemic lupus erythematosus has become wider and now includes many cases without rash, which previously were more difficult to diagnose. With the increased awareness of the protean nature of the disease it is likely that further familial cases such as those presented here will be recognized.

Summary.

Two familial cases of lupus erythematosus are described. The daughter had discoid lupus erythematosus whilst the mother developed systemic lupus erythematosus nine years later.

We wish to thank Dr. Una Ledingham for advice and permission to report Case 2, Professor K. R. Hill for his report on the liver biopsy in Case 2, Dr. A. D. Porter of St. John's Hospital for Diseases of the Skin and Dr. M. C. Aston of Bethnal Green Hospital for their help with Case 1.

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BOOK REVIEWS.

The Mast Cells.*

The book is divided into two parts. The first is a review of the literature mainly up to 1950 when the work described in the second part began. The second part is essentially the thesis "Functions of the Tissue Mast Cells" for which Dr. Riley was awarded the degree of Doctor of Philosophy by the University of St. Andrews. Dermatologists are warned forthwith that there is little or nothing in this book which concerns the clinical aspects of urticaria pigmentosa and other mast cell diseases.

It is, however, a most interesting story, told in a clear and careful manner, of how Dr. Riley and his colleagues step by step built up the evidence which has now proven beyond all reasonable doubt that tissue mast cells are responsible for the elaboration of histamine. But more than this, Riley believes that the mast cell is not solely responsible for heparin, nor histamine, but rather that this cell is a functional component of connective tissue and that indeed the mast cell is related functionally to connective tissues—"the common denominator which determines the presence of mast cells in an organ is the extent to which that organ contains loose, well-vascularised connective tissue". This is very far removed from the concept which was virtually accepted up to the beginning of Riley's work, namely, that mast cells, perivascular in distribution, produced an anticoagulant which they poured into the circulating blood. Slowly, in a logical manner, the evidence was built up. First by a detailed examination of the distribution of mast cells in cattle and rats, the number of mast cells in a given tissue being related not so much to its content of thin-walled capillaries, but to the presence in it of blood vessels with a substantial adventitial coat of mesenchymal cells. Secondly, a study of the effects of histamine liberators on the mast cells of the rat, for example, the demonstration that fluorescent histamine liberators, when applied to fresh spreads of peritoneum from intravitally stained animals, rapidly discharged the dye from the granules, after which the mast cells disintegrate. Then the combined histological and pharmacological examination of histamine in tissue mast cells, first in normal tissues, then in pathological conditions, including material obtained from urticaria pigmentosa and from the mast-cell tumours of domestic animals (surprisingly difficult to obtain at the time the work was done). These conditions all demonstrated that an excessively high mast-cell content of the tissue was associated with a correspondingly high histamine value, to such an extent that in the case of tumours, histamine assay of an organ proved to be as accurate a method as histological examination for the detection of distant metastases. Work with the specific histamine-liberator compound 48/80 on the mast cells of the rat demonstrated that a tissue depleted of its histamine by this histamine liberator is devoid of mast cells and that the recovery or return of mast cells is accompanied by reappearance of assayable histamine. More work dealt with the nature of the mast-cell granule and the binding of histamine within the mast cell. Finally, non-mast-cell histamine was studied, and the high histamine content of the pyloric mucosa demonstrated.

The work was started as an investigation into the significance of mastocytosis in pre-cancerous mouse skin (Dr. Riley is a Consultant Radiotherapist), but soon became involved with the details of histochemistry, pharmacology, comparative

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* *The Mast Cells.* James F. Riley (1959). Edinburgh and London: E. and S. Livingstone Ltd. Pp. 182. Illus. 65. Price 30s.

anatomy and histology, and the degree of proficiency shown by Dr. Riley in all these various specialities is most praiseworthy. There are more than 400 references in the excellent bibliography.

Dr. Riley is to be congratulated on this production which will be of immense value to those interested in the "riddle of the mast cells". The publication is of the usual high standard associated with the firm of Livingstone Ltd.

J. M. B.

Cancer of the Skin.*

A MAGNUM OPUS has been due for some time from Australia, the home of the solar keratosis and rodent ulcer, but we must call the latter a rodent carcinoma according to the author who would add squamous carcinoma and malignant melanoblastoma to his suggested nomenclature. We wish him luck in this crusade. There is, however, no doubt as to the success which his book will achieve. It is entirely excellent.

As is well known his material is vast. Over the last five years out of a total of 11,000 private patients, 740 were rodent carcinomas and approximately 1,300 pre-malignant conditions. Out of the same total of hospital patients 1,700 rodent carcinomas and 2,000 pre-malignant. The work which has been involved in writing this monograph was on the same heroic scale. The references occupy thirty-seven pages. Whilst one must be grateful for this vicarious labour the constant appearance of authors' names in the text somewhat mars smooth reading. There are some novel features. In his preface the author lists nineteen points with page references "to which I feel particular attention should be drawn". These are all more or less new ideas or different emphasis resulting from the author's experience. The cream of the book, as it were, can be skimmed by the lazy reader in a few minutes. Again after the pages of references there is a Stop-Press section from "recent literature and personal discussion while the main manuscript was in the final stages of publication". How few of us would have been so dogged.

The first two thirds of the book deal with all aspects of rodent carcinoma and squamous carcinoma including a very full section on keratoacanthoma. The magisterial touch from long experience is much in evidence. In a very full section on treatment while all methods are fully dealt with, the author's personal choice is clearly for x-ray therapy. His methods are fully described, treatment being almost entirely fractional with a preference for a maximum increment of 300 r. He quotes some excellent results where bone has been involved. Interest will be aroused by his full description of the combined cautery and podophyllin painting technique. This has been employed over the last six years on early lesions, over the last four years Synkamin (vitamin K powder) has been used instead of the podophyllin. The results are said to be excellent but no figures are given of the follow-up; probably time has not been sufficient. "Scalpel surgery" gets very slight reference. The author is fairly dogmatic that in so far as cosmetic results are concerned x-ray and radium offer distinct advantages over other results. He shows, however, a photograph with depressed x-ray atrophy and pigmentation with the comment "this is always a probable aftermath eventually even for correctly given doses". In the text, however, he refers to it as possibly appearing in some individuals who tend to be of the plethoric and often obese type. Stress is laid on the great value of hydrocortisone and antibiotic ointment as a regular application for x-ray reaction and superficial radionecrosis. No mention is made of the possibility of neomycin sensitivity of which a number of examples have been appearing in this country when neomycin has been used for this purpose.

* *Cancer of the Skin.* JOHN C. BELISARIO (1959). London: Butterworth and Co. (Publishers) Ltd. Pp. 321, illus. 201. Price £2 10*s*. 0*d*.

The section on what he calls " pseudo recurrences "—unusual manifestations such as milia, keratosis, occurring at the edge or outside of the treated area is interesting. In the reviewer's experience it is the first time these have been adequately and completely described. It is also interesting to note that he regards formication as a fairly reliable diagnostic point in early rodent or early recurrence. The remaining one third of the book deals with malignant melanoblastoma, sarcoma, and the reticuloses. In the author's words " it is necessary to draw on the recorded experiences of others in an attempt to clarify and portray the over-all picture " since no single observer can cover the field. Though these sections are also complete and concise the lack of the magisterial touch makes them a less attractive part of the book. The general presentation and numerous photographs are of a very high standard. The book is a " must" for the dermatologist's library. H. W. G.

Practical Dermatology.*

The first edition of Professor Lewis's book was published in 1952, under the title *Practical Dermatology for Medical Students and General Practitioners.* The new edition contains at the end an additional chapter on basic sciences. This appears to have been hurriedly written, and is ill-balanced. The section on virology is little more than the glad tidings that viruses can now be grown on tissue cultures. In the section on anatomy, whereas there is no mention of disintegration of nuclei in the description of the stratum granulosum, the student and general practitioner are told that, during growth stages, the hair papilla stains metachromatically, is Schiff-reactive and contains alkaline phosphatase. None of these phenomena are explained or their significance indicated. This is a common fault in the book, cf. Kveim test, p. 149. Some sentences defeated the reviewer, e.g. " The numerical increase of cells can be applied as a description of the epidermal cells (acanthosis)" (p. 340).

There are some astonishing views and statements. Acne pustules are attributed to pyococci. In rosacea, it is averred that if dilute hydrochloric acid, 10 minims t.d.s. (average dose), does not give good results, the diagnosis should be questioned. " Psychosomatic " appears to be used synonymously with severe neurotic excoriations, which are said to be rarely seen on the face. " X-ray therapy has a selective action on the exudate present in the affected skin " (p. 37).

The section on eczematous dermatoses is very confusing. After spending nine lines explaining why it is worth while retaining the term " eczema " and paying respects to its Greek derivation, the author tells us : " The terms ' eczema ' and ' dermatitis ' are herein used synonymously." " The chief difficulty in the diagnosis of contact dermatitis is differentiating it from other types of eczema."

In the treatment of atopic eczema (neurodermatitis), it is advised that X-ray therapy should be reserved for acute exacerbations.

Allotment of space is glaringly disproportionate. Whereas papular urticaria is dismissed in three lines, lichen nitidus gets eighteen, and ochronosis ten.

In the Dermatological Formulary, anhydrous lanolin is stated to have a high sensitizing index, whereas there is no such caution regarding formaldehyde.

The black and white illustrations are very numerous, but rather small and crowded together.

General practitioners may find the book handy for suggestions for treatment, but one can hardly recommend it for students. W. N. G.

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* *Practical Dermatology.* George M. Lewis. Second edn. (1959). London : Saunders. Pp. 363, 121 black and white plates. Price 56*s*.

A Synopsis.*

Although there is doubt in the reviewer's mind as to the usefulness of synopses nd similar students' aids, there is none as to the high quality of this example of the roup.

The preface states that the book is intended for the busy practitioner and for the tudent about to take his final examination. It must be judged as a book of reference –no one could read a synopsis. It should contain a mass of accurate information, et down as briefly as possible and readily found. This book achieves these require- ients, the last because the index is excellent. The busy practitioner, concerned with reatment as much as with diagnosis, may be disappointed for inherent in a book of his type is lack of detail. This leads to some frustration. For example, in the reatment of acne vulgaris he reads that lotio alba may be applied or Vleminckx's olution (liq. calcium sulph.) with lotio alba. Unless he knows what lotio alba is (it s not in the list of lotions in the formulary at the end of the book) he is in a difficulty nd anyway must guess how much of Vleminekx's solution should go with it, or onsult the Extra Pharmocopoeia. There is, nevertheless, a mass of useful information n this book which seems remarkably free from errors. The term zoster ophthalmicus nstead of herpes ophthalmicus is unfortunate (zoster is a girdle) and the description f a varioliform variety of parapsoriasis is misleading as it is generally agreed that is an entirely different condition. The first chapter well summarizes the anatomy nd physiology of the skin and there are useful lists of drug eruptions, of occupations nd the irritant substances associated with them and of concentrations and vehicles or patch testing. S. T. A.

Atlas de Dermatologie.†

The eighteenth section of this atlas includes a full monograph on leg ulcers ; this the diagnostic label preferred by the authors in view of the multiplicity of causative actors, rather than a name such as " varicose ulcer " which stresses only one aspect. he term " leg ulcer " is thus intended to cover all ulcers of the lower part of the leg hich depend upon local malnutrition or vascular upset, excluding those of more recise aetiology—a somewhat vague group from which individual entities such as lcerated nodular conditions can be rescued from time to time. This is not to minimize ne importance of venous incompetence, but rather to emphasize that in most cases etiology is multiple, different factors being present in every variation of proportion. n the course of this very thorough and well documented chapter, lesions of the erforating veins are mentioned, but the more specific ankle blow-out to which rockett drew attention is not clearly set out.

The photographs of this section are all rather blue—acrocyanosis, erythrocyanosis, aynaud's disease, chilblains, and leg ulcers. A good picture of Degos's *papulose aligne atrophiante* will be a useful reference for anyone who is thinking of diagnosing his very rare disorder. F. R. B.

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* *A Synopsis of Skin Diseases.* Bethel E. R. Solomons, jun. (1959). Bristol : ohn Wright and Sons Ltd. Pp. 304, 14 illus. Price 30*s*.

† *Atlas de Dermatologie.* Part XVIII. P. de Graciansky and S. Boule. Paris : ibrarie Maloine S.A. For reviews of previous sections see this Journal **65**, 105 ; **3**, 32 ; **67**, 266 ; **68**, 341 ; **70**, 188 ; **71**, 40.

Current Literature

NEUROTROPHIC ULCERS OF THE FEET. P. J. Kelly and M. B. Coventry. (1958) *J. Amer. med. Ass.*, **168**, 388.

Forty-seven patients with neurotrophic ulcers of the feet were thoroughly investigated. Diabetics with an inadequate peripheral circulation were excluded, but diabetics still accounted for 23 cases, myelodysplasia for 8, syringomyelia 6, old spinal cord or sciatic injuries 6, peripheral neuritis 1, neuropathy of herpes zoster 1, and tabes dorsalis 1. The ulcers in diabetics were usually confined to the region of the metatarsal heads and the medial aspect of the hallux; those which followed cord lesions were commonly on the heel. The clinical features are described. Radiological examination may assist diagnosis and should perhaps be a routine procedure in diabetics. Conservative and prophylactic measures are important. For chronic ulcers under the metatarsal heads removal of the toe and metatarsal head or of the metatarsal head alone was sometimes of lasting benefit. Simple débridement of the ulcer may be sufficient. The authors emphasize that the presence of occlusive vascular disease must radically alter the programme of treatment.

A. J. R.

SIDE-EFFECTS NOTED IN TREATMENT WITH METHYLPREDNISOLONE (MEDROL). F. G. McMahon and E. S. Gordon. (1958) *J. Amer. med. Ass.*, **168**, 1208.

Methylprednisolone was given to 67 patients and 10 healthy volunteers for an average period of $4\frac{1}{2}$ months. Disturbances of body weight occurred in 40 subjects with obesity in 14; acne developed in 9, and mental changes in 8. Other side effects are tabulated. The side effects were comparable to those observed with prednisone and prednisolone, but methylprednisolone has perhaps a greater anti-inflammatory effect.

A. J. R.

SUBUNGUAL HEMORRHAGE IN PAN WASHERS. P. I. Long, Jr. (1958) *J. Amer. med. Ass.*, **168**, 1226.

Three men employed as pan-washers developed subungual haemorrhages. They wore heavy rubber gloves. It is suggested that the combination of trauma and an unexplained action of detergent solution trapped in the gloves may be responsible for this unusual symptom which was not observed in those who did not wear gloves. Sensitivity to rubber was excluded

A. J. R.

TRIAMCINOLONE IN THE TREATMENT OF SYSTEMIC LUPUS ERYTHEMATOSUS. E. L. Dubois. (1958) *J. Amer. med. Ass.*, **167**, 1590.

Twenty-nine patients with systemic lupus erythematosus were treated with triamcinolone. The clinical response was very similar to that obtained with the older steroids, all the clinical and laboratory abnormalities disappearing except long-standing renal involvement. Eighteen patients showed slow progressive weight loss. The cutaneous side effects, particularly Cushingoid appearance, hirsutism and striae were more marked than with older steroids. Muscle weakness which developed in 6 patients from 4 to 32 weeks after the start of treatment was the most serious side effect. Of 14 patients who had previously been treated with other steroids 7 were better controlled with triamcinolone.

A. J. R.

PATHOLOGIC PATTERNS OF THE SEBACEOUS GLAND. J. S. Strauss and A. M. Kligman (1958) *J. invest. Derm.*, **30**, 51.

A histological study of the reactions of the sebaceous gland to all sorts of injury inflicted on the skin: for example occlusion with adhesive tape, allergic dermatitis, the application of carcinogens and chlornaphthalene, dermabrasion, the injection of irritants, colchicine and thallium acetate and, on the pilosebaceous organ itself, plucking, needle puncture and electrolysis. The characteristic reaction, like that associated with physiological occlusion by a comedo, is regression of the gland to undifferentiated epithelium.

J. H. T. D.

SULPHYDRYL OXIDASE ACTIVITY IN SKIN HOMOGENATES. H. R. Rony, G. J. Scheff, D. M. Cohen and W. R. Rennagel. (1958) *J. invest. Derm.*, **30**, 43.

The processes involved in keratinization are supposed to include hydrolysis of cytoplasmic amino acid groups, thereby liberating sulphur-free amino acids and exposing —SH groups, the for-

mation of disulphide cross linkages, the formation of hydrogen bonds, and the carbohydrate metabolism required to supply the energy for keratin synthesis.

The only part that we know much about, the sulphydryl oxidase reaction, is not specific to the epidermis nor is it consistently associated with any specific epidermal activity such as the hair growth cycle. The skin homogenates used in this experiment appeared to contain factors that both accelerate and inhibit this and other oxidation processes and act differently from those prepared from other organs.

Although the findings here described offer no promise of a facile determination of these speculations, the paper makes delightful reading and provides encouragement to further effort.

J. H. T. D.

THE EFFECT OF AMINO ACIDS ON THE GROWTH AND SPORULATION OF TRICHOPHYTON RUBRUM : POSSIBLE APPLICATION TO DIAGNOSIS AND THERAPY. Margarita Silva. (1958) *J. invest. Derm.*, **30**, 69.

A detailed study of the value of 26 different amino acids as the source of nitrogen for colonies of five different strains of *T. rubrum* on glucose agar slopes. A sixth strain had completely different preferences and is not reported. J. H. T. D.

INFLUENCE OF VARYING PHYSICAL FACTORS ON PATCH TEST RESPONSES. W. A. Anderson, H. Shatin and O. Canizares. (1958) *J. invest. Derm.*, **30**, 77.

This work was inspired by nonspecific reactions of the skin to a more or less bulky solid object applied in the form of a patch test. (Similar considerations no doubt apply to plaster of paris bandaging.) The effect of shape, the rounding off of edges and the influence of pressure on the reaction to allergens are studied.

Pressure on the patch test appeared to enhance the reaction to an allergen ; (and yet it so often seems in clinical practice that shoulderstraps, garters and footwear tend to extinguish it!)

J. H. T. D.

THE QUANTITATIVE NUTRITIONAL REQUIREMENTS OF THE GENUS MICROSPORUM. E. S. Bereston, H. H. Robinson and Shirley A. Williams. (1958) *J. invest. Derm.*, **30**, 63.

Of the *Microspora canis*, *Audouini* and *gypseum*, an exact number of spores having been sown in a semisolid dextrose agar in flasks each containing one of 21 different amino acids or of some other source of nitrogen, the 17-day-old mycelial felt was separated and weighed dry. It is demonstrated that hydroxyproline is inhibitory, that certain amino acids are better sources of nitrogen than others ; that caseine hydrolysate and Sabouraud give 3–30 times as much growth as any of the single sources of nitrogen ; and that these organisms are autotrophic of any vitamins that may be necessary to them. J. H. T. D.

RESPIRATION OF HUMAN SKIN. NORMAL VALUES, PATHOLOGICAL CHANGES AND EFFECT OF CERTAIN AGENTS ON OXYGEN UPTAKE. E. Leibsohn, B. Appel, W. C. Ullrick and M. J. Tye. (1958) *J. invest. Derm.*, **30**, 1.

Skin obtained by punch biopsy from non-dermatological patients and from the apparently normal skin of patients with skin diseases was cut tangentially into slices, each of which would consist more or less of the epidermis, and incubated in the Warburg manometer. The results, which closely compare with other similar experiments and with tracer estimations of fat metabolism, show that the energy requirement of the skin is about 7% of the whole body at rest, and that the epidermis accounts for 4% of it or 10 times as much as the dermis bulk for bulk dry weight.

J. H. T. D.

EOSINOPHIL ATTRACTING SUBSTANCES (EOSINOTAXINS) EXTRACTED FROM HUMAN EPIDERMIS. R. B. Stoughton. (1958) *J. invest. Derm.*, **31**, 59.

Epidermis removed *in vitro* by heating for 1 min. at 55° C. (thermal damage), by freezing and stretching, or with the razor, and incubated with or without trypsin, then ground and filtered, provided the materials that were compared with trypsin by itself, digests of albumin or casein and various amino acids. An intradermal injection into human skin was followed 2 hours later by biopsy. Unfortunately it was possible to make only one experiment on each individual subject so that results have to be interpreted with reserve.

The subjects who received doses of their own epidermis frozen and sliced, both of them treated with trypsin and incubated produced 47% and 17% of eosinophils. Thermal damage plus incubation gave 18%. But the other experiments including the one receiving epidermis incubated without trypsin failed to show more than 2% of eosinophils in the infiltration. J. H. T. D.

THE COMBINED USE OF TREPONEMIN SKIN TESTING AND SPECIFIC SEROLOGICAL TESTS IN THE DIAGNOSIS OF SYPHILIS. R. W. Pearson, J. Portnoy, H. J. Magnuson and A. H. Wheeler. (1958) *J. invest. Derm.*, **31**, 75.

Evidence is produced that the positive treponeme immobilization and complement fixation tests, restored by (presumably by way of antigenic stimulus) an injection of killed *Treponema pallidum*, can be relied on.

The Treponemin skin test has limitations similar to that of Luetin. J. H. T. D.

ELECTRON MICROSCOPE STUDY OF EPIDERMOPHYTON FLOCCOSUM. E. L. Laden and J. O. Erickson. (1958) *J. invest. Derm.*, **31**, 55.

Very little in the way of internal structure—some cytoplasmic granules thought possibly to be mitochondria but nothing that could be called a nucleus—could be seen in sections of material fixed in osmic acid and embedded in perspex. A slightly different but no more satisfactory picture was yielded by extraction with potassium permanganate. J. H. T. D.

SKIN CHLORIDES IN DERMATITIS HERPETIFORMIS AND PEMPHIGUS. Z. Felsher. (1958) *J. invest. Derm.*, **31**, 47.

Using punch biopsy material from 5 cases of D.H., 3 of pemphigus vulgaris, 3 of unclassified pemphigus, 1 of p. foliaceus and 13 cases of non-bullous dermatoses the author failed to find significant differences in the chloride content of dry fat-free skin. He reviews some recent literature concerning the influence of halogens in the bullous diseases. J. H. T. D.

MORPHOLOGIC CHANGES IN PILOSEBACEOUS UNITS AND ANAGEN HAIRS IN ALOPECIA AREATA. E. J. Van Scott. (1958) *J. invest. Derm.*, **31**, 35.

In addition to an exemplary and delightful histological study illustrated by cross sections of the hair follicle, the strangely inaesthetic objects obtained by 3-dimensional realization of the pilosebaceous apparatus are used to demonstrate the arrest in Anagen IV characteristic of the malady. J. H. T. D.

STUDIES ON THE PERCUTANEOUS ABSORPTION OF C^{14} LABELLED STEROIDS BY USE OF THE GAS-FLOW CELL. F. D. Malkinson. (1958) *J. invest. Derm.*, **31**, 19.

The quantity of radioactive steroid absorbed was calculated from that remaining on the surface of the treated skin.

Testosterone gets through normal skin, hydrocortisone only after stripping and cortisone not at all.

The same method can be used to determine the time required for regeneration of the barrier destroyed by stripping. J. H. T. D.

PENICILLINASE-PROVED ALLERGY TO PENICILLIN IN POLIOMYELITIS VACCINE. M. C. Zimmerman. (1958) *J. Amer. med. Ass.*, **167**, 1807.

Penicillin is present in many poliomyelitis vaccines in concentrations varying from 1 to 200 units per ml.; others contain less that ·001 units per ml. Six allergic reactions provoked by the vaccine in patients already highly sensitive to penicillin are reported. The role of the penicillin was established by the rapid clearing of the reaction with penicillinase and by the lack of reaction to a penicillin-free vaccine. Penicillin-free vaccines should be used for patients known to be sensitive. A. J. R.

BIOLOGICAL FALSE-POSITIVE RESULTS IN SEROLOGIC TESTS FOR SYPHILIS. G. W. Waring, Jr., A. S. Lanes and H. Mescon. (1958) *J. Amer. med. Ass.*, **168**, 2004.

The Treponema pallidum immobilization test (T.P.I.) was carried out in 75 patients giving repeated positive serological reactions for syphilis. No patients had signs or a history of syphilis. The 52 negro patients all had positive T.P.I. reactions; of the 23 whites only 39% had positive reactions. The epidemiological implications are discussed and it is concluded that the margin of error of the T.P.I. test is probably small. A. J. R.